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THE  
VASO-MOTOR SYSTEM

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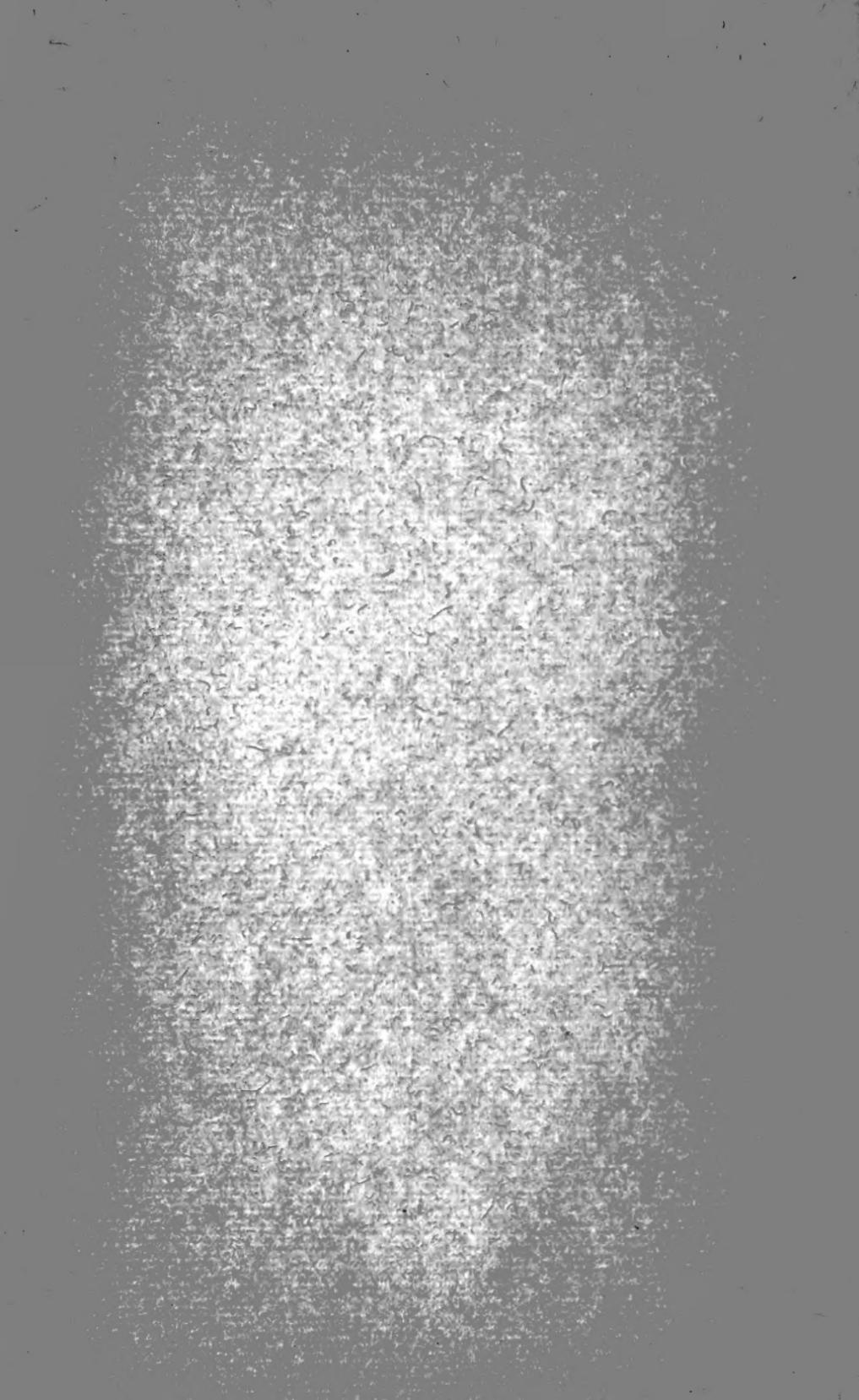


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# THE VASO-MOTOR SYSTEM

BY

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## *EDITOR'S PREFACE.*

In no science is the advance at any one time general. Some sections of the line are pushed forward while other parts may remain for years with little movement, until in their turn they are enabled to progress in consequence of the support afforded by the advance of the adjacent sections. The increasing number of series of monographs in different sciences is a recognition of this fact, as well as of the concentration of interest which characterises this age of specialisation.

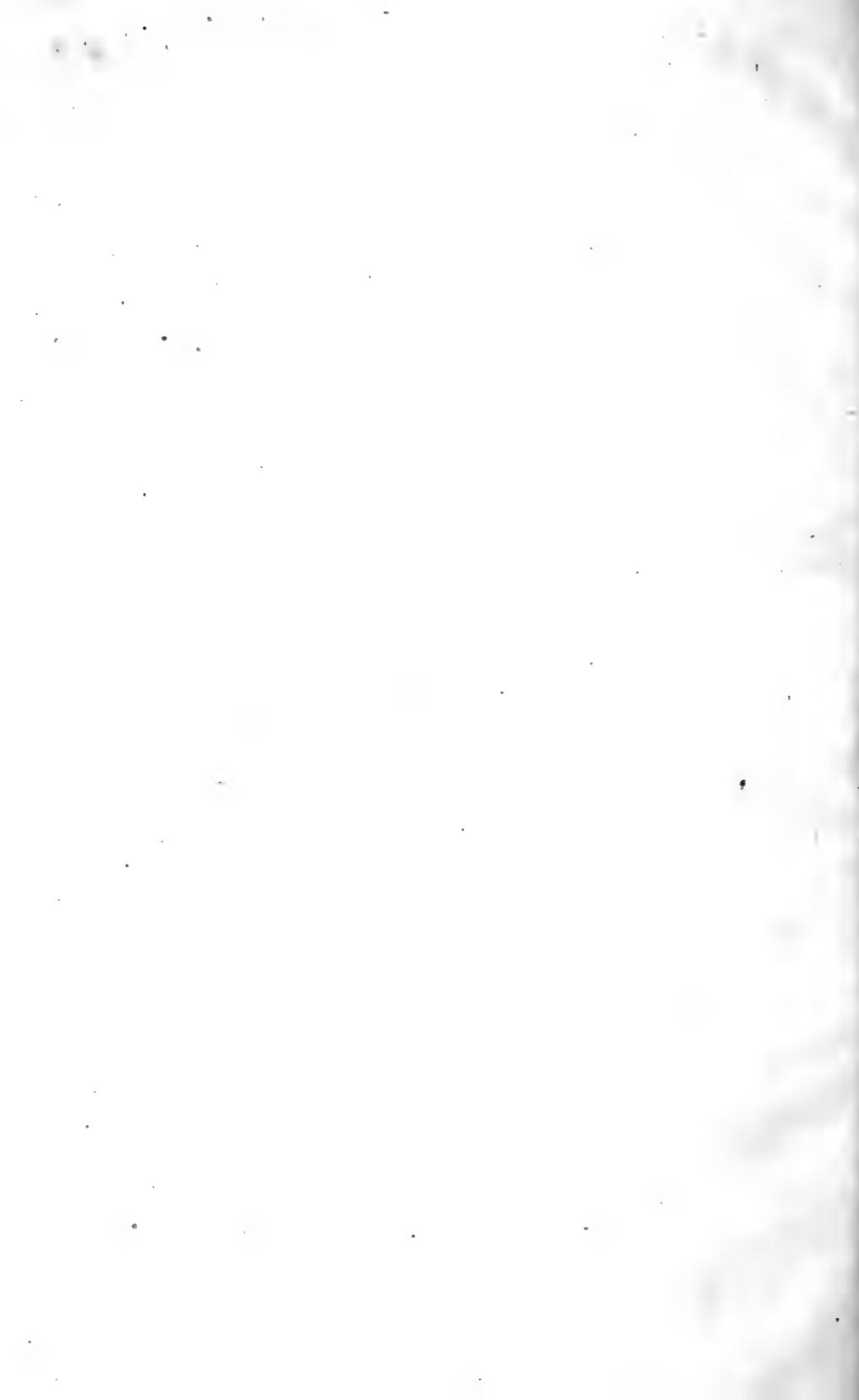
In the present series it is intended to set out the progress of physiology in those chapters in which the forward movement is the most pronounced. Each monograph will contain an account of our knowledge of some particular branch of physiology, written by one who has himself contributed in greater or less degree to the attainment of our present position. It is hoped that by securing the help of men who are actively engaged in the advance of the subject the outlook of each monograph will be forwards rather than backwards. An exhaustive account of previous writings on the subject concerned is not aimed at, but rather an appreciation of what is worth retaining in past work, so far as this is suggestive of the paths along which future research may be fruitful of results. The more valuable the monographs in inspiring the work of others, the greater will be the success of the series.

ERNEST H. STARLING.

1941

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## *INTRODUCTORY.*

It is proposed in this monograph to discuss the various factors which produce changes in the diameter of the blood vessels. Thus, not only the action of nerves, but also that of chemical agents, will be included. The heart, although an integral part of the mechanism of the circulation, requires the space of a special monograph. In the present one, the heart is assumed to be beating at a constant rate and with a uniform output, so that our problem is to investigate how, under these conditions, the blood pressure is modified by changes in the calibre of the blood vessels and how the blood supply of individual organs is regulated in correspondence with their needs in different degrees of activity.

## CHAPTER I.

### *THE STRUCTURE AND GENERAL PROPERTIES OF THE BLOOD VESSELS.*

---

#### *STRUCTURE.*

The *arteries* and the *veins* are each composed of several coats (see Fig. 1). The most internal is a smooth layer of epithelial cells. In the figure, that of the artery is in folds, owing to the contraction of the muscular coat in the process of preparation. Outside the epithelial coat, we find

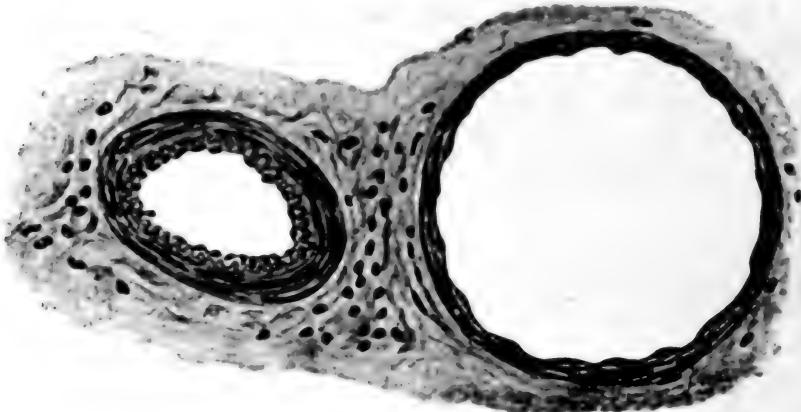


Figure 1.

Transverse section of a small artery (on the left) and of a small vein (on the right).  
 $\times 250$ . (Schafer's "Essentials of Histology".)

a layer of that kind of muscle cell known as non-striated or smooth muscle. This varies in thickness, being, relatively to the other coats, best developed in the small arteries,

although it is also present in small amount in the veins. The constituent fibres are almost entirely arranged in a circular direction around the blood vessel. Between the internal and the muscular coats, there is a layer of elastic tissue. In the largest arteries, such as the aorta, the muscular coat is of less importance than in the arterioles. In

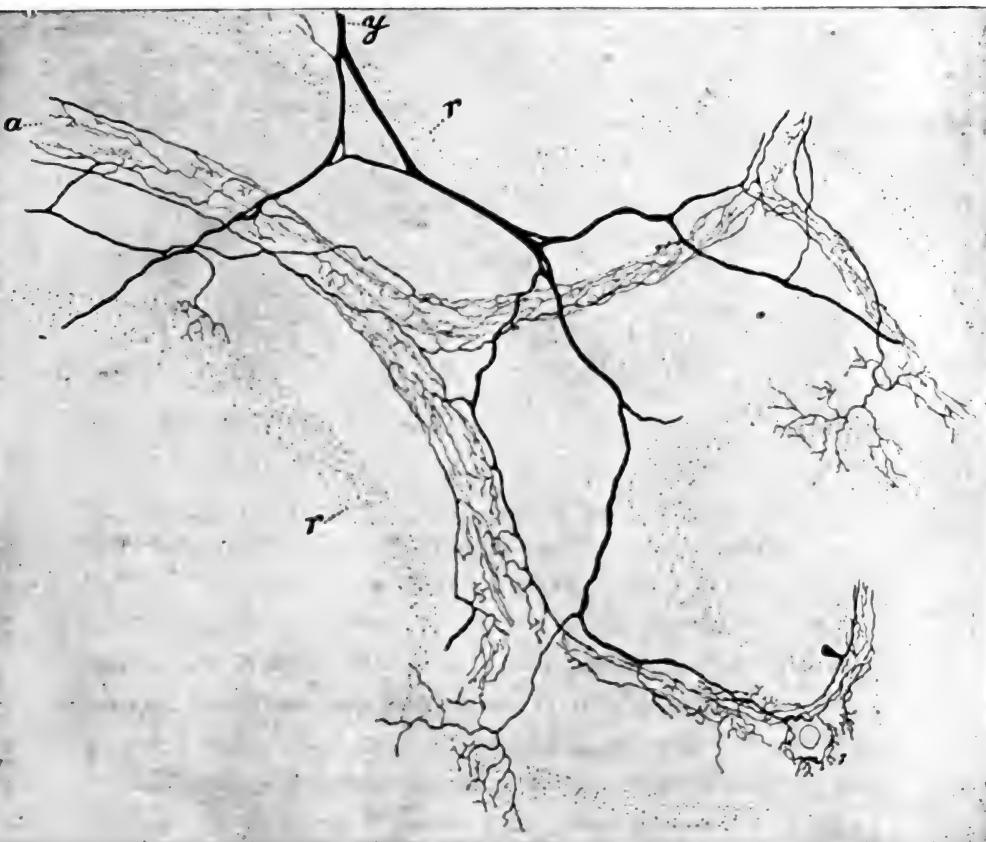


Figure 2.

Plexus of nerves around a small artery of the Spleen. Golgi's method.

- a* Artery, surrounded by branched nerve fibres, which end freely.
- y* Nerve from which the plexus arises.
- r* Pulp substance. The broad white space around the artery is the Malpighian substance. In places, nerve fibres are seen passing to the pulp.

(Retzius, 1892, Taf. XXI Fig. 1).

these larger arteries, layers of elastic tissue are intermixed with the muscular coat. Outside of all, there is a sheath of ordinary connective tissue, sometimes containing, especially in the large veins, a few muscular cells.

The *capillaries* consist of delicate tubes of thin epithelial cells only. In the liver, it appears that they are, for the most part, mere intercellular channels, not possessing complete walls of their own and having extensions into the interior of the liver cells (Sutherland Simpson). The contractility of the capillaries will come up for discussion later. (See p. 19.)

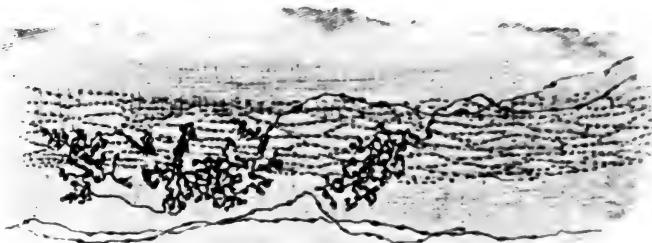


Figure 3.

Terminal ramifications of afferent nerve fibres in a small blood vessel (Dogiel). (Quain's Elements of Anatomy. Vol. II Pt. I = Schafer's "Textbook of Microscopic Anatomy".)

Although the muscular coat is itself elastic, the special function of the *elastic layer* in the arteries is to accommodate, by stretching, the blood sent out by the heart in systole, and, by the arterial recoil during cardiac diastole, to ensure a nearly continuous flow of blood in the smaller vessels. It is elasticity, also, which enters as chief factor in the rate of propagation of the pulse-wave; but this does not concern us in the present work.

The *muscular coat*, being actively contractile, has the important part to play of regulating the calibre of the vessels, especially of the small arterioles. In order that they may

be under the control of the central nervous system, the cells of this coat are supplied with efferent nerves, both excitatory and inhibitory, sometimes copiously (Fig. 2 p. 3).

There are also sensory nerves to blood vessels. The appearance of the receptor endings is given in Figure 3.

As to the function of these receptors, it is well known that a reflex fall of blood pressure is produced by stimulation of certain nerves in the arch of the aorta, but the function of those from the smaller arteries is somewhat problematical at present.

#### *THE PERIPHERAL RESISTANCE.*

As long as the output of the heart remains constant, the height of the arterial pressure varies with the resistance encountered by the blood current in the peripheral vessels. If the blood were able to flow out as rapidly as it is sent in by the heart, there would, clearly, be very little pressure in the arteries. While if the blood is unable to flow out as fast as the cardiac systole drives it in, owing to a resistance to its outflow, the arteries become stretched and the internal pressure rises until it forces out the blood at an average rate equal to that at which it is supplied by the heart. As remarked above, the object of the muscular coat and its control by nervous and other influences is to adjust this peripheral resistance, and for two objects — to change the general arterial pressure on the one hand, and on the other to modify the blood-supply to an individual organ, when the change in calibre is limited to the vessels of this organ.

It is necessary to remember that the resistance opposed by a number of narrow channels is greater than that offered by a single large channel of sectional area equal to the sum of the smaller ones. This is stated, correctly, to

be due to the greater friction in the latter case. But the friction is not between the wall of the blood vessel and the blood, but between the constituent elements of the liquid itself (see Unwin, 1911, p. 35). The existence of this internal friction was realized by Newton and is an aspect of the mutual attraction of molecules which gives rise to the phenomena of cohesion and to the  $\alpha$  factor of the Van der Waals' equation of state. In the case of liquids, it causes the property known as viscosity. We see then how the peripheral resistance in the vascular system is directly proportional to the viscosity or internal friction of the blood. Why is it then that the resistance is greater in a number of narrow channels, the arterioles, than in a smaller number of large channels, arteries, of equal sectional area, or even, within limits, a smaller sectional area?

When a liquid is flowing through a tube, the layer in contact with the wall of the tube is to all intents and purposes at rest, while that in the centre has the greatest velocity. Each layer is exposed to friction with the more rapidly moving layer next it; thus the velocity decreases progressively from the centre until the wall of the tube is reached, where the friction holds the outermost layer at rest. Practically, therefore, all the friction is between the layers of the liquid itself. Suppose that the tube is wide; the actual thickness of the peripheral layer, in which the increase of velocity from zero to its maximum takes place, only occupies a small part of the total space, so that the greater part of the contents is moving at the same maximum rate and experiencing no perceptible internal friction. Such is the case with the large arteries. In the arterioles, on the other hand, a much larger proportion of the cross section is occupied by liquid experiencing friction; the layer in which the velocity continues to increase may reach to the centre of the tube. Thus the whole volume

of the blood in the arterioles may be exposed to friction, whereas only a small fraction of it is so exposed in the larger arteries (see diagram in the author's "Introduction to General Physiology" p. 145).

When the capillary area is reached, the total width of the bed becomes somewhere about one-thousand times that of the aorta (see Fig. 4), so that the rate of flow is very

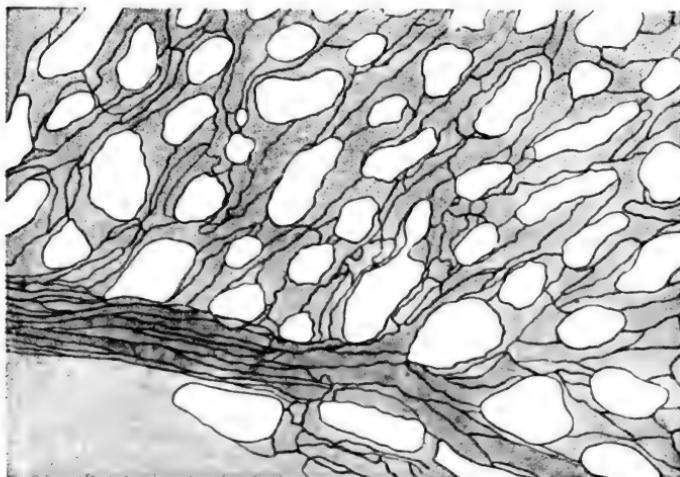


Figure 4.

Small Arteriole Breaking up into Capillaries.

From lung of frog Outlines of cells brought out by  $\text{AgNO}_3$  (Mann).

(From Quain's Elements of Anatomy. Vol. II Pt. I = Schafer's "Textbook of Microscopic Anatomy".)

To show the copious network of capillaries and somewhat sudden transition of arteriole to capillary.

small. The friction being nearly proportional to the velocity (Unwin, 1911, p. 61), is accordingly very small in this region, as compared with that in the arterioles. The work of Krogh (1919), to be referred to more in detail in Chapter IV, shows that in some areas many of the capillaries may be closed when the cells supplied by them are inactive. The relative sectional area of arterioles and capillaries thus varies largely.

It is difficult to say to what extent the bed increases before the capillaries are reached, but observation of the circulation in the web of the frog's foot suggests that it is not very great, the flow in the smallest arterioles being enormously more rapid than that in the capillaries.

We may take it then that the chief resistance is experienced in the arterioles and the importance of this fact for our present purpose is that these vessels possess a well developed muscular coat, under the control of nerves. Their lumen can thus be narrowed and the resistance to the flow of blood increased; at the same time, the supply of blood to the capillaries fed by them is decreased.

It is stated that the muscular coats of the small and smallest arterioles consist of cells arranged circularly only. The larger arteries have also a small number of muscle fibres arranged longitudinally. The function of the longitudinal muscle is doubtful, but it is clear that it is the circular coat of the small arteries which is of importance for regulating purposes.

In connection with the application of Poiseuille's law to the flow of blood in narrow channels, it is necessary to remember that blood is not a homogeneous liquid and that the suspended corpuscles are subject to deformation. The viscosity, therefore, is not the same in capillary tubes as in tubes with a diameter equal to several times that of the corpuscles. The relation of this fact to statements as to the non-applicability of Poiseuille's law to the circulation is discussed in a paper by Hess of Zürich (1915).

#### *TONE OF ARTERIOLES.*

In order to be able to understand the factors which regulate the size of the arterioles, it is necessary to know what is the state of their muscular coat when deprived of

all connection with the nerve centre; or, in other words, what is their condition when free from outside influence. If we divide the nerves supplying an organ, say the submaxillary gland, and prepare the vein so that the amount of blood issuing from it can be measured, we find that, after the effect of section of the nerves, which stimulates them, has passed off, the rate of flow becomes constant.

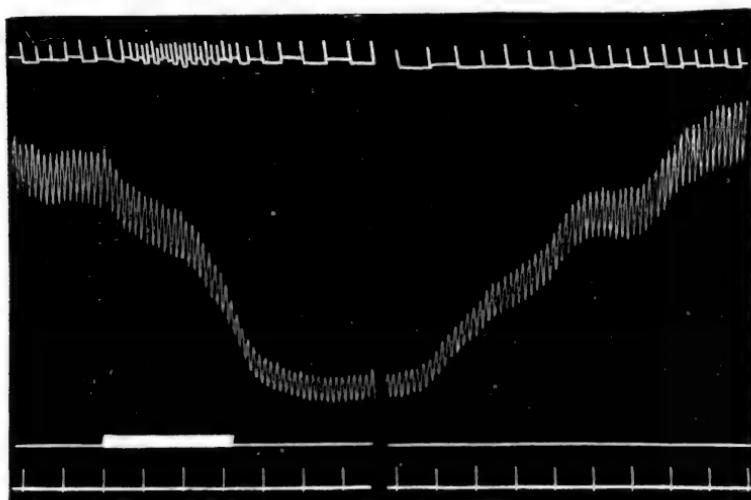


Figure 5.

Effect of (reflex) stimulation of the chorda tympani nerve on blood flow through the submaxillary gland.

Sympathetic supply cut.

Upper trace — Drops of blood from gland vein.

Lower trace — blood pressure.

Upper signal — stimulation of central end of vagus of the opposite side.

Lower signal — time in 10 second intervals.

(Bayliss. 1908. 2. Fig. 1.)

We then stimulate the sympathetic nerve to the gland and notice that the rate of flow from the vein is greatly reduced. This is as we should expect if this nerve contains fibres which cause the muscular coat of the arterioles to contract, as we know that it does. But what happens when

we stimulate the chorda tympani nerve going to the gland? We notice in fact an immediate large *increase* in the rate of flow from the vein (Fig. 5). We can only explain this by a widening of the arterioles. If their diameter can be increased, as well as diminished, it must be that when left alone the muscular coat is in a state of contraction, of a moderate degree, and that this contraction can be made greater by certain nerves and made less, or relaxed, by certain other nerves. Fig. 6 illustrates the fact by another method.

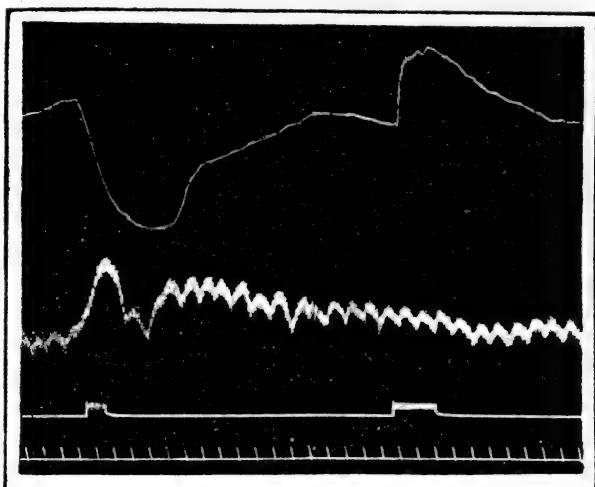


Figure 6.

Effect on the vessels of the tongue of the dog produced by stimulation of the vaso-constrictor and of the vaso-dilator nerves to it.

Upper trace — volume of the tongue, a fall means decrease of volume, due to constriction of arterioles.

Lower trace — arterial pressure, to show that the changes in the tongue are not due to changes in the pressure of the blood.

At the first mark on the upper signal line, the peripheral end of the cervical sympathetic nerve was stimulated. At the second rise, the peripheral end of the lingual nerve.

Time marked in ten-second intervals.

This behaviour of the smooth muscle of the blood vessels is not strange, since we meet with it in other

situations, as Fig. 7 shows. It seems to be a natural property of this kind of muscle.

Further evidence of the existence of a natural "tone" in the arterial muscle is given by the results of Goltz and Freusberg (1874, p. 175). They divided the sciatic nerve in dogs and noticed that the temperature of the paralysed paw was at first higher than that of the normal one, owing to vascular dilatation whose cause will be discussed later.

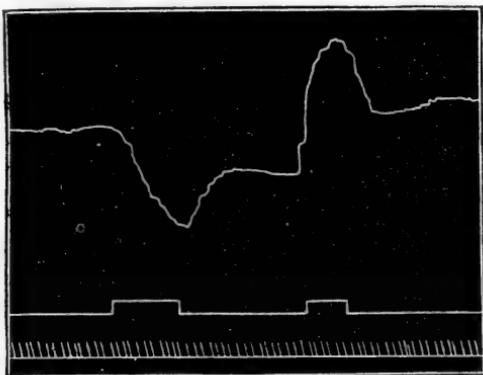


Figure 7.

The retractor penis muscle of the dog.

At the first signal, the muscle lengthens owing to stimulation of the pelvic nerve.

At the second signal, the pudic nerve causes contraction.

But after a few days, the temperature of the two paws became nearly equal and after some weeks that of the paralysed paw was sometimes lower than that of the normal one, although the nerve supply had not been reestablished. This can only mean that the normal "tonus" had returned spontaneously.

The existence in the sciatic nerve of fibres which cause dilatation of the vessels of the paw was shown by Goltz, Freusberg and Gergens (1876, p. 62). The dilatation which occurs on section of the nerve was enormously increased by snipping the nerve with scissors, a very effective means

of mechanical stimulation. This is a further proof that the blood vessels do not entirely relax when deprived of their nerve supply.

#### VASO-MOTOR NERVES.

That the effects of nerve stimulation on smooth muscle are produced by direct action on the muscle cells, and not through the intermediation of ganglia, was clearly demonstrated by Pavlov (1885). The adductor muscle of *Anodonta* is usually in a state of tonic contraction, but it can be made to relax by the stimulation of certain nerves. It then remains in this state until the stimulation of certain other nerve fibres excites it to contract again. There are no nerve cells between any of these fibres and the muscle itself, so that the two opposite influences must be exerted on the muscle itself directly. Pavlov points out that there must be two distinct ways in which the different kinds of nerve fibres terminate, in order that one set may excite, the other inhibit. In the claw of the crayfish, two nerve fibres of different aspect can be seen terminating in one and the same muscle fibre (Mangold, 1905).

In the case of the arterial muscle, the nerves causing contraction are known as *vaso-constrictors*, those causing relaxation or inhibition of muscular tone are *vaso-dilators*. Both together are included in the name, *vaso-motor*. The former set are excitatory as regards the muscle; the latter, *inhibitory*. To avoid confusion, it is well to speak of "stimulating" either kind of nerve when we act upon it in such a way as to set it into activity. When the nerve impulses, which, so far as all evidence goes, are identical in both kinds of nerve fibres, reach the muscle, the effects they produce differ according to the manner of termination there.

## *ACTION OF CHEMICAL AGENTS.*

Similar effects to those of the two kinds of nerve fibres can be produced by chemical agents, or drugs, acting on the blood vessels themselves. Thus Figure 8 shows the

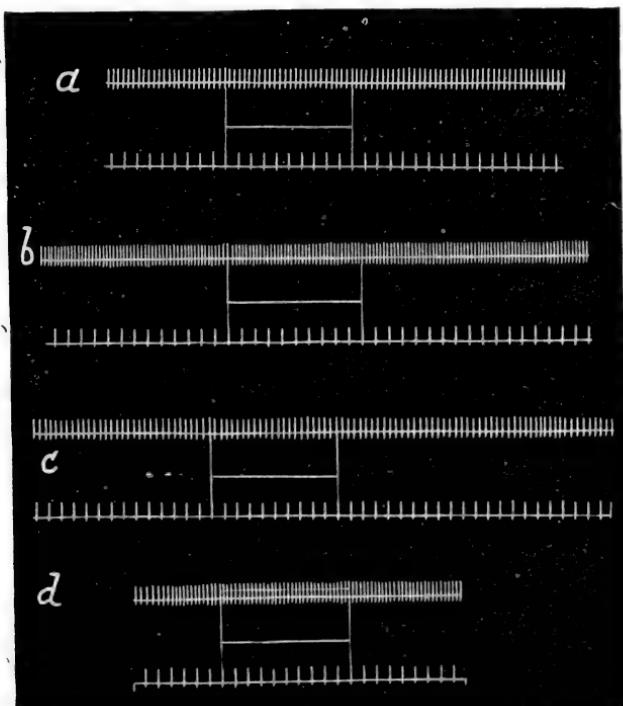


Figure 8.

Action of Carbon Dioxide on the Blood Vessels of the Frog. Hind legs perfused with Ringer's solution. Upper tracing in each (*a*, *b*, *c* and *d*), gives the drops issuing from the veins. Lower tracing-time in ten seconds.

- a* Normal. 25 drops in 100".
- b* Ringer's solution saturated with CO<sub>2</sub>. 38 drops.
- c* Normal again. 22 drops.
- d* Carbon dioxide again. 33 drops.

dilatation produced by acid and Figure 9 p. 14 shows the constriction produced by adrenaline.

## RHYTHMIC CONTRACTIONS.

Under certain circumstances, the blood vessels exhibit another aspect of intrinsic activity, apart from the influence of the nervous system. The muscular coat undergoes a series of rhythmic contractions and dilatations. This was seen in the veins of the bat's wing by Wharton Jones

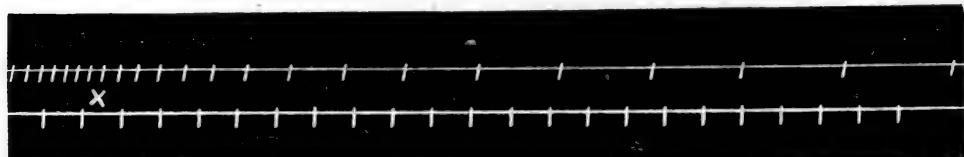


Figure 9.

## Action of Adrenaline.

Frog's legs perfused. Adrenaline added at X. The drops fall at longer intervals.

(1852) and is a common property of smooth muscle in various situations, as the wall of the intestine. It is especially manifest in the beat of the heart and has been occasionally seen in arterioles (Fig. 10). Stimuli, such as

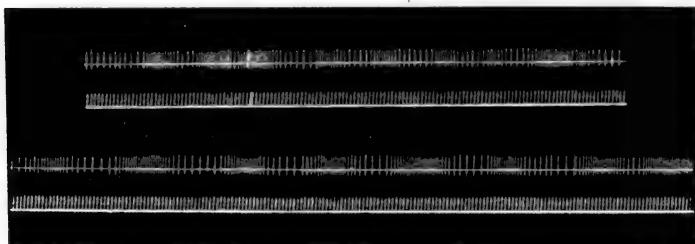


Figure 10.

Perfusion of Whole Frog, Pithed, with Ringer's Solution.

Drops fall in rhythmic groups.

distension, warmth, or certain chemical reagents, are apt to set it into activity.

*REACTION TO STRETCHING.*

Smooth muscle in various situations has been shown to respond to the stimulus of stretching by contraction. Such cases are the muscular tube of the earthworm (Straub, 1900), and the stomach of the frog (Winkler, 1898). The frog's heart sometimes ceases to beat when empty, but can be excited to contraction by distension with liquid. Wharton Jones (1852) noticed that the rhythmic contractions of the veins of the bat's wing are directly dependent on the pressure within them. Certain phenomena noticed in blood vessels have been interpreted as due to similar properties. In the course of experiments made for other purposes, I found that the volume of a limb whose nerves were cut was at first increased by a rise of arterial pressure, as would naturally be expected. But this distension was followed, on return of the blood pressure to the original level, by a contraction much beyond that which corresponded previously to this height of blood pressure (Bayliss, 1902). At the time when these experiments were made, it was not known that the suprarenal gland could be stimulated through its nervous supply to send out adrenaline into the blood stream. This was shown by Elliott (1912). Anrep (1912) pointed out that all the methods used in my experiments were such as might cause a secretion of adrenaline and that it is unnecessary to assume a contractile response of the arterial muscle to distension. This fact does not, of course, exclude the possibility of such a response and the explanation of the opposite reaction to decreased tension is not quite so satisfactory. Figure 11 shows the large relaxation produced in the arterioles of the limb in consequence of a fall of pressure produced by brief closure of the femoral artery. This is regarded by Anrep as being due to the production of vaso-dilator substances in con-

sequence of deficient oxygen supply. No doubt, such a result does happen from prolonged cutting off of blood supply, but in the experiment of the figure the animal was under curare with vigorous artificial respiration and the stoppage of the circulation only lasted for eight seconds. Further, there was very little difference between the effects

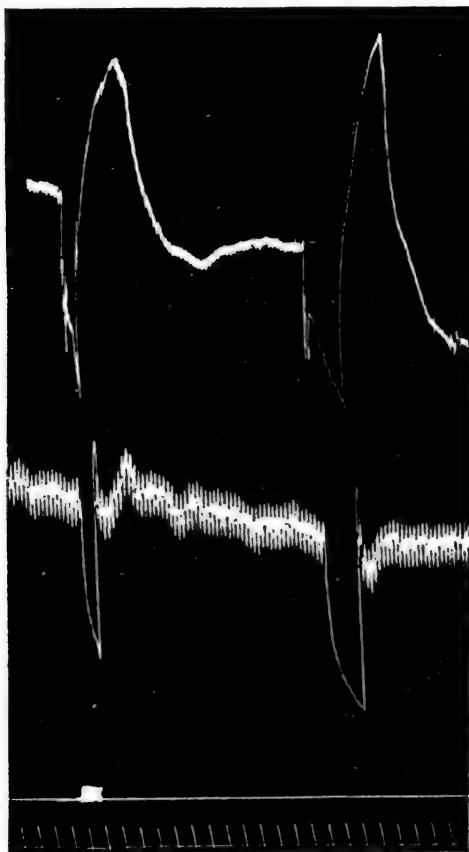


Figure 11.

Local Reaction of Blood Vessels to Fall of Internal Pressure.

Upper curve — volume of hind leg of dog, nerves cut.

Lower curve — pressure in femoral artery.

Time in 10 sec. interval.

The abdominal aorta was compressed twice, the first time only being marked by the signal.

of the eight seconds and of twenty seconds closure of the artery. Recent experiments with isolated arteries have shown me that it is very difficult to obtain one that is capable of stimulation either by chemical or electrical means, so that the failure of distension to produce a contraction in the experiments of this kind done by Anrep is not a serious objection. It may be pointed out that if the asphyxia theory is not a satisfactory explanation for the case of the reaction to decrease of internal pressure, it follows that the vessel was previously in a state of contraction owing to distension. On the whole, I fear that we must regard the question as undecided.

• *THE "PERIPHERAL HEART" THEORY.*

Connected with the problem of the preceding paragraph is the view put forward by Hürthle (1912, 1913) that the blood is assisted onwards by a contraction of the arteries behind each pulse wave. It was found that the rate of flow through an artery was, in certain conditions, greater than could be brought about by the mere difference of pressure between its ends. The amplitude of the pulse wave was also found to be increased as it passed onwards in the living animal, as contrasted with its behaviour in the dead one, where it decreased in the way that would be expected. The interpretation of these facts is difficult and Hess (1916) has subjected the theory of the "peripheral heart" to a severe criticism, pointing out that such a contraction of the artery would be effective only if it were great enough to close the lumen entirely. On the other hand, Carl Tigerstedt (1913) found that if two electrodes were placed on the carotid artery there was an electrical response of the arterial muscle to each heart beat, of such direction as to indicate the progression of a wave of con-

traction towards the periphery. If this muscle does actually respond to stretching, it is quite possible that it does so to distension by the pulse wave, but the result can have no physiological significance, so far as the mass movement of the blood is concerned. It is to be remembered that the pulse wave is not the same thing as the mass movement. The former is the progression of an elastic wave at a much greater rate than the blood itself flows.

Hess was unable to obtain evidence of contractile response in isolated arteries and it appears from his work on the viscosity of heterogeneous liquids in relation to their rate of flow that Hürthle's work did not take sufficient account of the special laws followed by such systems.

#### *PROPERTIES OF SURVIVING ARTERIES.*

McWilliam (1902) showed that arteries removed from the body maintain their excitability for several days, if kept in cold Ringer's solution. Such preparations are very useful for testing the direct action of drugs. Observations on the properties of excised arteries have also been made by Kesson (1913). He finds that exposure to cold does not in itself lead to contraction, but that when contraction is brought about by mechanical or electrical stimulation, this contraction may persist for days in the cold. It disappears when the preparation is warmed to  $38^{\circ}\text{C}$ .

Tested by the application of internal pressure, contracted arteries respond by slow relaxation and gradually return to the contracted state when the pressure is removed. When an excised artery is to be used for testing the effect of drugs, or other stimulation, it is necessary to relax the muscular "tone" by the application of a weight or tension. A particular value of this weight is required in each particular case, and this must be found by experiment. (See

Meyer, 1906; Macht, 1915.) Whether the giving way to pressure is always a true relaxation is not clear. The nature of the "contraction" itself is somewhat obscure. Thus, while one artery may be distended by a pressure of 20 mm of mercury, another, apparently in the same state of contraction, may require 140 mm (Kesson, 1913, p. 269). We are reminded of the behaviour of certain "tonic" muscles of the invertebrate (see my "Principles of gen. Physiology, pp. 534—539). In these latter muscles, a state of shortening can be maintained without the production of a tensile elastic stress and, as it appears, without the expenditure of energy. It has been suggested (Bethe, 1911) that the "tonus" of the arterioles in the mammal has a similar nature, since, if the mechanism were like the tetanus of skeletal muscle, one-sixth to one-quarter of the whole resting energy-consumption would be situated in the arterioles.

Further investigation of this contractile mechanism seems necessary. The apparent contractile response to stretching, as well as the somewhat puzzling effects of certain drugs, may find their explanation therein.

The effects of chemical agents on excised blood vessels will be described in a later chapter.

**Note.** During the passage of this monograph through the press an important paper on the structure of capillaries has been published by Vimtrup (1922) from the laboratory of Prof. Krogh. The presence of strongly branched contractile cells, first described by Rouget in 1873, is confirmed. These cells lie on the outside of the endothelial wall and sometimes almost completely encircle the capillary. The contraction of a capillary is seen to begin at one or more of these cells. Although they are sometimes elongated, their general appearance reminds one rather of pigment cells than of muscle cells, but their function is clearly that of controlling the lumen of the capillaries.

## CHAPTER II.

### *THE GENERAL ANATOMICAL ARRANGEMENT OF THE VASO-MOTOR NERVES.*

The nervous mechanism of control of the blood vessels will best be considered to begin with; because, in general principle, the phenomena are simpler than those where chemical agents are concerned. In the latter case, we have the complication of three possible points of attack—the nerve-centres, the neuro-muscular junctions and the muscle itself.

#### *VASO-CONSTRICCTOR NERVES.*

As Gaskell (1885) showed, the origin of these nerves from the central nervous system is entirely confined to the white rami forming the sympathetic system (see especially Gaskell's monograph, 1916, pp. 31—36). This area extends from the first or second thoracic to the fourth or fifth lumbar segments inclusive. Vaso-constrictor nerve-fibres are contained in all the white rami. It is remarkable that these fibres are distributed to all parts of the body, not only to the thoracic and upper lumbar regions, but to the head and to the hind-limbs.

The evidence for the statement that there are no vaso-constrictors other than those of sympathetic origin is intimately connected with the action of adrenaline, a compound produced by the activity of the supra-renal bodies. The question will be discussed more fully in Chapter V

and it may suffice to mention here that the suprarenals are developed in intimate relationship with the sympathetic system and that wherever there is known to be a supply of sympathetic nerve fibres to any organ, it is found that adrenaline produces the same effects as stimulation of the sympathetic nerves, as pointed out by Langley (1901, p. 256). So uniformly is this the case that adrenaline may be spoken of as a test for sympathetic innervation. In the case of the vaso-constrictor nerves, if adrenaline fails to cause constriction of the arterioles in any organ, we feel justified in saying that this organ is devoid of a vaso-constrictor supply.

The following is a brief summary of the facts known with regard to the vaso-constrictor innervation of various parts of the body. Further details may be found in the papers quoted. Figure 12 gives a diagrammatic scheme.

*Stomach and Intestine.* Fibres to the cardiac end of the stomach are given off from the 5<sup>th</sup> to the 9<sup>th</sup> thoracic segments (Langley, 1903, p. 849).

The small intestine receives fibres from the 5<sup>th</sup> thoracic to the 3<sup>rd</sup> lumbar, occasionally from the 4<sup>th</sup> lumbar (Fr. Franck and Hallion, 1896; Bunch, 1898 as regards viscero-motor fibres).

*The Pancreas.* 6<sup>th</sup> thoracic to 1<sup>st</sup> lumbar (Franck and Hallion, 1897).

*The Spleen.* 3<sup>rd</sup> thoracic to 1<sup>st</sup> lumbar (chiefly from the 5<sup>th</sup> to the 10<sup>th</sup> thoracic (Bulgak, 1877; Schafer and Moore, 1896).

*The Liver.* The branches of the portal vein in the liver are supplied from the 3<sup>rd</sup> thoracic to the 11<sup>th</sup> thoracic, chiefly from the 5<sup>th</sup> to the 9<sup>th</sup> thoracic (Bayliss and Starling, 1894; Edmunds, 1915).

Suppose that the lateral pressure in the portal vein is being measured and that a particular spinal nerve, which contains constrictor fibres to the intestine, is stimulated.

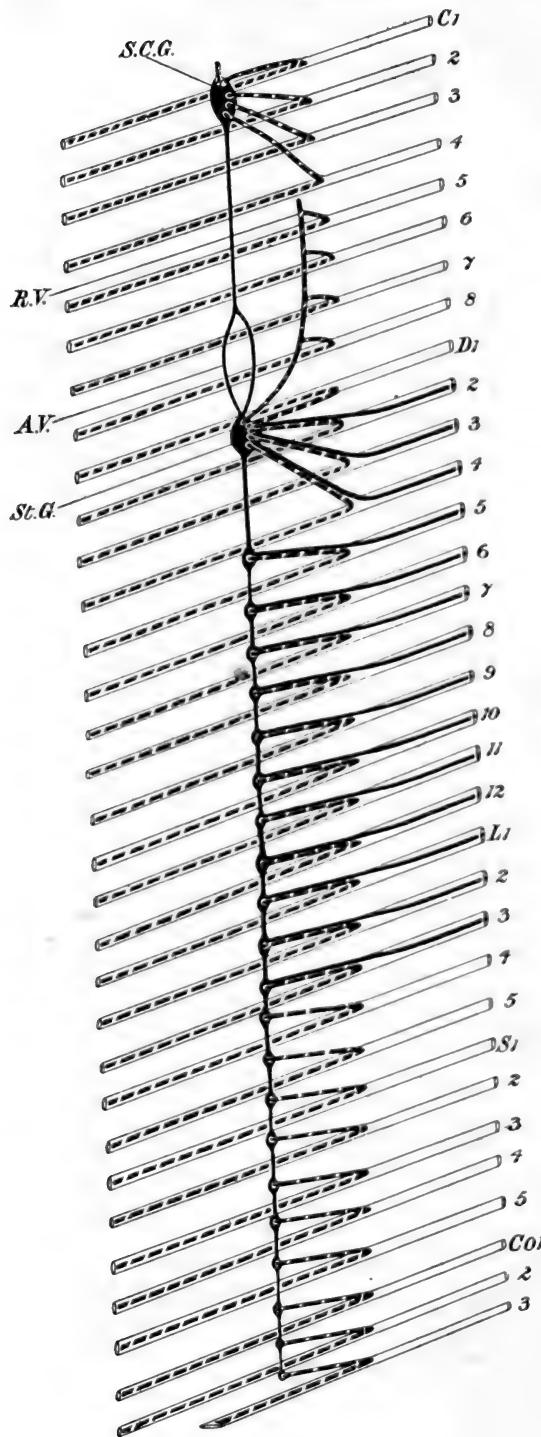


Figure 12.

## Origin of the Vaso-constrictor Nerves.

On the right, the anterior roots of the spinal nerves from the first cervical to the 3<sup>rd</sup> sacral, and from the 2<sup>nd</sup> thoracic to the 3<sup>rd</sup> lumbar, inclusive, forming the sympathetic system leave in the roots from the 2<sup>nd</sup> thoracic to the 3<sup>rd</sup> lumbar, inclusive. The lateral sympathetic chain further includes prolongations of these processes from ganglion to ganglion. Certain ganglia are fused together. These connector fibres (== white rami) form synapses with excitatory neurones in the ganglia, giving off the post-ganglionic fibres (dotted) which form the grey rami and also join the spinal nerves for distribution. The white rami contain the vaso-constrictor fibres for the whole of the body, but those for the abdominal and pelvic viscera form their synapses in ganglia situated more peripherally than the lateral chain (Gaskell, 1916, p. 18).

It is easy to see that the portal pressure must fall, owing to reduced inflow of blood, if the vessels in the liver remain unaltered in calibre (Figure 13). If, on the contrary, this pressure is seen to rise, as in Figure 14, the fact must be due to constriction in the liver beyond the place where

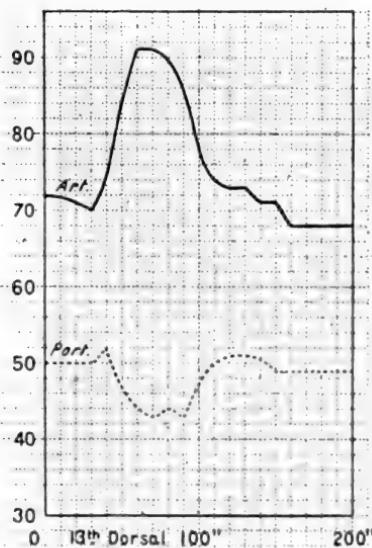


Figure 13.

Constriction of Intestinal Arterioles and Portal Pressure.

Upper curve-arterial pressure.

Lower curve-lateral pressure in splenic vein.

Stimulation of 13<sup>th</sup> thoracic root.

(Bayliss and Starling, 1894.)

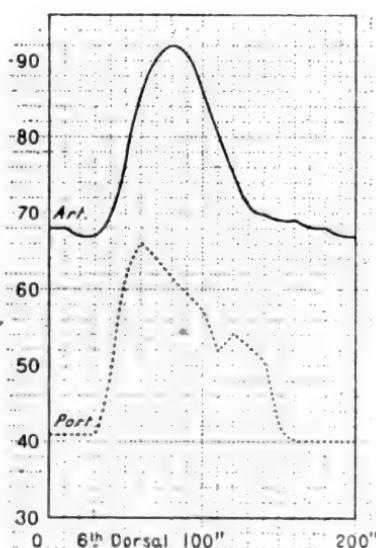


Figure 14.

Constriction of Portal Vessels in the Liver.

Upper curve-arterial pressure.

Lower curve-pressure in splenic vein.

Stimulation of 6<sup>th</sup> thoracic nerve root.

(Bayliss and Starling, 1894.)

the pressure is measured. The effect of this constriction must more than compensate for the reduced inflow of blood. The ultimate branches of the portal vein have, doubtless, more similarity to veins than to arteries; but, since they break up into capillaries, they perform a similar function to that of arterioles in controlling the blood supply to the cells.

*The Kidney.* Chiefly from the 6<sup>th</sup> to the 13<sup>th</sup> thoracic inclusive, a few fibres in the 4<sup>th</sup> and 5<sup>th</sup> thoracic (Bradford, 1889).

A point of morphological interest is the large number of segments from which these fibres arise. The origin of the kidney from a long series of segmental organs will be remembered.

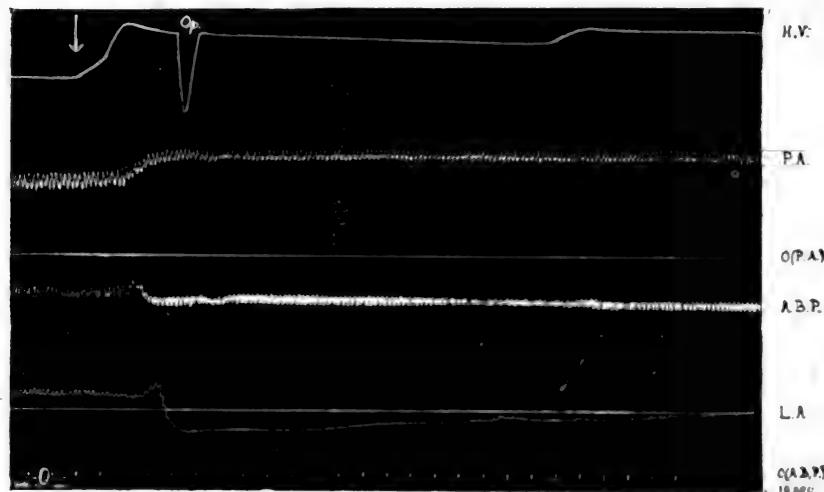


Figure 15.

Effect of Adrenaline on Pulmonary Circulation.

Heart-lung preparation. Adrenaline added at the arrow.

1<sup>st</sup> trace from top—heart volume.

2<sup>nd</sup> do — pressure in pulmonary artery, rises owing to constriction of lung arterioles.

3<sup>rd</sup> do — zero of pulmonary pressure.

4<sup>th</sup> do — pressure in aorta, no rise because the resistance was fixed.

5<sup>th</sup> do — pressure in left auricle. Falls owing to diminished inflow from lung. Bottom line — time in 10 sec. intervals. (Fühner and Starling, 1913, p. 301.)

*The Lungs.* According to Bradford and Dean (1894), the lungs are supplied with vaso-constrictors from the 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> thoracic roots inclusive, a few are contained in the 6<sup>th</sup> and 7<sup>th</sup>. Later work, especially that of Brodie and Dixon (1904), made it doubtful whether there is any vaso-

motor supply to the lungs at all. The question was decided by Fühner and Starling (1913), who showed that adrenaline constricts the branches of the pulmonary artery, so that the sympathetic sends vaso-constrictor fibres to them (see Figure 15 and Tribe, 1914).

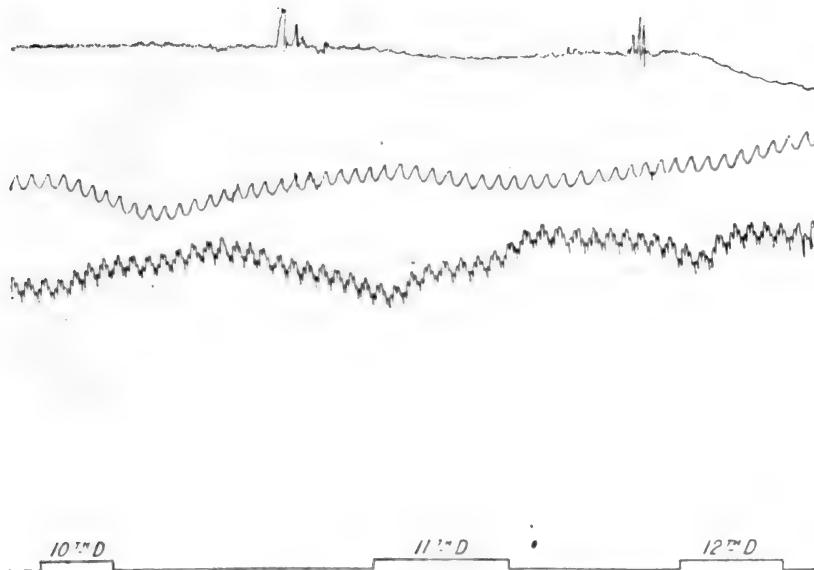


Figure 16.

## Vaso-constrictors of Limbs.

Top trace — Volume of hind-limb.

Middle trace — Volume of fore-limb.

Bottom trace — Arterial pressure.

Stimulation of 10<sup>th</sup> thoracic root gives constriction in fore-limb only.

That of 11<sup>th</sup> root — slight constriction in both.

That of 12<sup>th</sup> root — in hind-limb only. (Bayliss and Bradford, 1894.)

*Pelvic Organs.* The innervation was worked out in detail by Langley and Anderson. The large intestine receives vaso-constrictors through the inferior mesenteric ganglion from the 3<sup>rd</sup> and 4<sup>th</sup> lumbar roots. The uterus — from the 2<sup>nd</sup> to the 4<sup>th</sup> lumbar (Langley and Anderson, 1895.) The external genital organs — 13<sup>th</sup> thoracic to 4<sup>th</sup> lumbar.

*The Limbs.* The fore-limbs — from the 3<sup>rd</sup> thoracic to the 11<sup>th</sup> thoracic. The hind-limbs — from the 11<sup>th</sup> thoracic to the 3<sup>rd</sup> lumbar, all inclusive (Langley, 1891; Bayliss and Bradford, 1894).

Figure 16 shows that slight constriction is produced in both fore- and hind-limbs by stimulation of the 11<sup>th</sup> root. The fact is of interest in connection with the embryological origin of the limbs as outgrowths of a continuous (Wolffian) ridge (Balfour, 1878, Vol. II, p. 153).

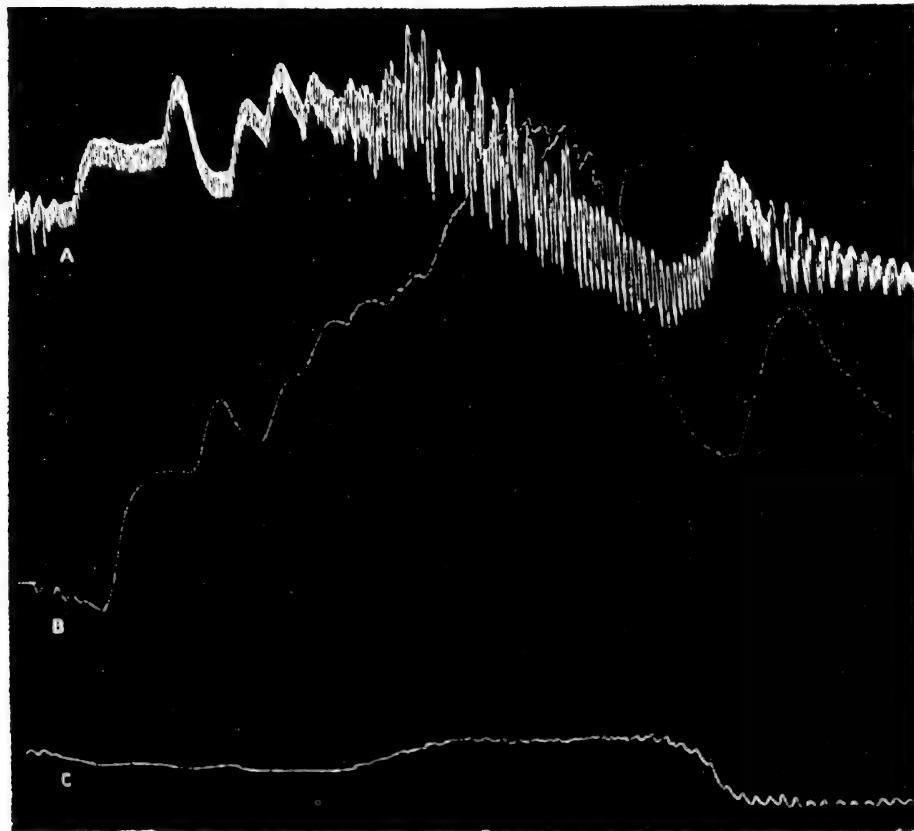
*The Trunk.* The organs of the head and neck receive constrictors from the 2<sup>nd</sup> to the 5<sup>th</sup> thoracic segments inclusive. But, as will be seen presently, the evidence for the supply of any fibres to the brain itself is very doubtful.

#### *ORGANS WITH MINIMAL OR NO VASO-CONSTRICCTOR SUPPLY.*

The absence of certain organs from the above list will probably be noticed. No satisfactory evidence of vasoconstrictor supply has yet been found for the brain or for the heart. The position of the voluntary muscles in somewhat uncertain.

The *cerebral Circulation* was found by Bayliss and Hill (1895) to be entirely dependent on the general arterial and venous pressures. In Figure 17, there is seen to be no indication of any fall in the venous pressure in the Torcular Herophili in the course of the general stimulation of the vaso-motor nerves in asphyxia. This pressure follows exactly the arterial pressure as far as X and then, owing to the failure of the heart and the resulting rise in venous pressure, it continues to rise still further, while the arterial pressure falls. This absence of vaso-motor supply is probably to be accounted for by the supreme importance of the central nervous system. Its blood supply can be in-

creased by raising the general arterial pressure, that is, by vascular constriction in other organs, which must be content with a diminished supply.



A. Carotid. B. Toreula Herophili. C. Right Auricle.

Figure 17.

Cerebral Circulation. Curarized and anaesthetized dog.

A Arterial pressure. Artificial respiration stopped at A.

B Pressure in Torculea Herophili (= cerebral venous pressure).

C Pressure in right auricle.

(Bayliss and Hill, 1895.)

*The Heart.* The blood supply of this organ is automatically varied in correspondence with its needs as the aortic pressure determines the flow through the coronary arteries.

Vaso-motor nerves to these vessels would seem superfluous. Adrenaline, however, causes a greatly increased blood flow through the heart vessels. This fact suggests the presence of dilators of sympathetic origin. But, as we shall see presently, the existence of such nerves is very doubtful and there is another explanation of the dilatation of the coronary vessels in the effect of the "metabolites" produced by the increased activity of the muscle brought about by adrenaline (Markwalder and Starling, 1913).

*The Voluntary Muscles.* So far as voluntary muscle receives any vaso-constrictor innervation, it will be found to follow that of the part of the body to which the muscle belongs, in accordance with the preceding list.

Gaskell states (1916, p. 90) that section of the abdominal sympathetic causes a great increase in the blood flow through the quadriceps extensor group of muscles, owing to the cutting off of constrictor impulses from the nerve centres. The experiments of Hartman, Blatz and Kilborn (1919) confirm those of Gaskell, since a thermometer inserted underneath the leg muscles showed a rise of temperature, sometimes lasting for an hour, after section of the nerves. It would seem that this rise could not be satisfactorily accounted for by vaso-dilatation in the skin and was too prolonged to be due to stimulation of dilators to the muscle by the injury of section. But it requires control by the use of a skinned limb and by freezing of the nerve without stimulation.

The chief regulation of the blood supply to muscles, however, is by vascular dilatation and will be discussed below. It is not easy to see what purpose vaso-constrictor nerves serve, except to assist in modification of the general blood pressure. The temperature of the body is almost entirely kept up by the oxidative processes in muscle, but the degree of this combustion is controlled by those cerebro-

spinal nerves which bring about contraction in various degrees, inclusive of the "tonus", or, as it is better called in agreement with Sherrington (1916), "postural contraction".

#### VASO-DILATOR NERVES.

The anatomical arrangements of these nerves are more irregular and dissimilar in nature than are those of the vaso-constrictors. No general statement can be made. Certain of the nerves arising from the bulbar region of the brain contain fibres which cause, in some way, the

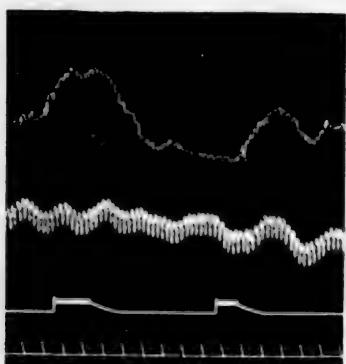


Figure 18.

Dilatation of the penis of the dog on stimulation of the pelvic nerve-roots.

Upper tracing—volume of the penis.

Lower do — blood pressure.

Two stimulations shown by the signal.

Time in 10 sec. intervals.

arterioles of the organs supplied by them to dilate. Such a nerve is the *chorda tympani*, arising from the Intermediate nerve of Wrisberg, which may be described as a typical vaso-dilator nerve. Similar nerves arise from the sacral cord in the pelvic system of nerves to involuntary muscles. The *nervi errigentes*, causing relaxation of the arteries in the corpora cavernosa and spongiosa of the penis, may be especially mentioned as belonging to this system (see Fig. 18).

Vascular dilatation, chiefly in the skin, is obtained when the peripheral ends of the cut dorsal roots of the limb plexuses are stimulated (Stricker, 1876). The same effect is obtained when the main trunks of these nerves are stimulated in a particular manner. The fibres responsible were shown by myself (1901) to be anatomically indistinguishable from the ordinary sensory afferent fibres, failing to degenerate when the roots are cut between the cord and the ganglion (Figure 19), but degenerating when the dorsal root ganglia are removed.

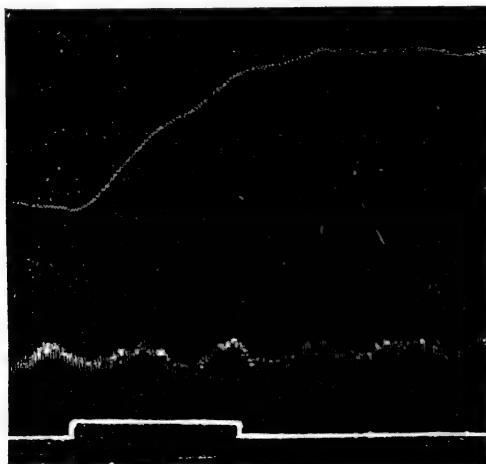


Figure 19.

Vaso-dilators to Hind-limb Intact after Section of Dorsal Root.

Upper trace—volume of limb.

Lower do — arterial pressure.

Stimulation of 7<sup>th</sup> lumbar root, eight days after section between cord and ganglion. (Bayliss, 1901, p. 189.)

They are very sensitive to mechanical stimulation and their presence in nerves which contain vaso-constrictors in addition, such as the sciatic, can thus be demonstrated. They appear to be identical with Head's "protopathic" fibres (see below). After removal of the dorsal root ganglia

and degeneration of the afferent fibres, no vaso-dilatation can be obtained from the sciatic nerve, so that it seems evident that the fibres in question form the only vaso-dilator supply to the limbs. The vascular dilatation produced in this way is called, on Langley's suggestion, "antidromic", on account of its being brought about by impulses passing along sensory fibres in a direction contrary to what is regarded as the usual one. There is some evidence that there is a similar state of affairs in the external ear of the rabbit, in the intestine and in the kidney; reference will be made to the latter below.

Interesting confirmation of the vaso-dilator effect of sensory fibres was obtained by Head and myself (unpublished). At a stage of regeneration of the radial nerve of the cat at which only protopathic sensory fibres were present, stimulation of the peripheral end caused an obvious dilatation of the vessels of the paw. The sympathetic fibres do not regenerate until some weeks later. This nerve contains no motor fibres for voluntary muscle and it sometimes happens that no (sympathetic) vaso-constrictor fibres are present in the normal nerve. In the latter case, stimulation causes vaso-dilatation. The absence of sympathetic fibres can also be ensured by removal of the stellate ganglion. We also performed this operation and found, after degeneration, a pure vascular dilatation on stimulation of sensory nerves to the limb.

The investigation of the vaso-dilator supply to the various parts of the body is rendered difficult by the fact that arterioles are dilated by the direct action upon them of acids and other chemical agents, as we saw above (Figure 8). In the case of the chorda tympani, for example, when we stimulate the trunk of the nerve, we set into activity the secretory function of the gland cells, which is associated with the production of carbon dioxide, etc. When,

therefore, we find that there is a simultaneous dilatation of the vessels, it has been argued that this is due to a direct effect of "metabolites", rather than to the presence of inhibitory nerve fibres to the vessels (Barcroft, 1914). It may be said that atropine paralyzes the secretory activity without stopping the vaso-dilatation. But we cannot be sure that all cell metabolism is stopped along with that involved in the secretion of saliva. Indeed, Barcroft (1914) obtained evidence of increased consumption of oxygen when the chorda tympani was stimulated under atropine, although the secretory activity was paralyzed. Admitting that production of metabolites may aid in the dilatation observed, it seems to me that Barcroft's results show a nervous effect in addition, since the degree of dilatation is not in proportion to the increase in the consumption of oxygen. Thus, a 109 % increase in the latter coincides with a 488 % increase in the former in one case, while, in another case, a 50 % increase coincides with an increase in rate of blood flow of 812 %; that is, a larger dilatation with a less consumption of oxygen.

The chorda tympani nerve also supplies fibres to the tongue, which cause vaso-dilatation therein. Anrep and Evans (1920) found that this dilatation may be present without any increase in oxygen consumption.

Some experiments by Anrep on the pancreas (unpublished) suggest, moreover, that the stimulation by metabolites is not a universal one. When a preparation of secretin, devoid of the impurity which causes fall of blood pressure, was used to set the gland into activity, there was little or no vaso-dilatation.

In the cat, a copious secretion of saliva is obtained when the cervical sympathetic is stimulated. This is associated with only a moderate degree of vaso-dilatation, but it is to be remembered that vaso-constrictor fibres are

being stimulated along with the secretory fibres. The drug ergotoxin, obtained by Dale from ergot (1906), was shown by him to paralyze secretory fibres but not vaso-dilator fibres. After ergotoxin, stimulation of the sympathetic fails to produce secretion from the submaxillary gland and, at the same time, the vaso-dilatation is absent. This is good evidence that gland activity in itself may produce vaso-dilatation.

Stimulation of the motor nerve to a voluntary muscle produces vaso-dilatation therein, as shown by Gaskell (1876). The fact that curare abolished the vascular effect along with the muscular contraction seemed to Gaskell to indicate that the products of metabolism were to be held responsible for the former. On the other hand, it was found that if the dose of curare was only just sufficient to abolish visible contraction of the muscle, mechanical stimulation of the nerve by a series of cuts ("crimping") was followed by increased blood flow. It was thought possible, therefore, that the vaso-dilator fibres might be paralyzed by the larger doses of curare, since there was evidence that the cardio-inhibitory fibres of the vagus and the nervi errigentes were so affected. Moreover, observation of the mylo-hyoid muscle of the curarized frog under the microscope showed that the arterioles were dilated on stimulation of the nerve to the muscle, although there was no trace of contraction. Special control experiments showed that this dilatation was not passive in consequence of reflex rise of blood pressure. The conclusion to which Gaskell arrives (1916, p. 90) is that the chief part of the vaso-dilatation is due to the acids produced, but that the presence of vaso-dilator fibres is possible. It is perhaps worth mention that the antidromic dilatation in the leg is not completely abolished by removal of the skin, so that the muscles appear to receive dilator innervation of this kind, to a small degree.

There are no glands or structures to which metabolic activity can be ascribed in the area of distribution of the *nervi erigentes*. Barrington (1913), indeed, finds no secretory fibres in the pelvic nerves; but that the hypogastric nerves contain a supply to Cowper's and Bartolini's glands. If the products of these glands were concerned with erection, it should be the hypogastric not the pelvic nerves which carried the vaso-dilators.

We may conclude that the whole of the phenomena of vascular dilatation can only be explained by the existence of genuine inhibitory nerves to the arterioles. As a general rule, in fact, we find that smooth muscle, or other muscle not subject to voluntary control, such as that of the heart, is supplied with nerves of two kinds, excitatory and inhibitory. Thus, the intestinal muscle is inhibited by the splanchnic, excited by the vagus; the iris is inhibited by the sympathetic, excited by the third nerve; the bladder is inhibited by the hypogastric, excited by the pelvic nerves; the heart is inhibited by the vagus, excited by the sympathetic and so on. Figure 7 serves to show the fact in the case of the *retractor penis* muscle. It is naturally to be expected that the vascular muscles would not form an exception to the rule.

We notice further that, in all these cases, the two kinds of nerve fibres arise from different regions of the central nervous system. Wherever we have definite knowledge of the source of the two kinds of fibres supplied to the vascular muscles, we find a similar diversity of origin. Since, as we have seen, all the vaso-constrictors arise from the sympathetic and from no other source, we should not expect to find any vaso-dilators of sympathetic origin. Nevertheless, certain experimental facts have been explained on this hypothesis and it will be instructive to examine the evidence in favour of it.

Dastre and Morat (1880), confirmed by Heidenhain and by Langley (see Gaskell, 1916, p. 93), found that stimulation of the cervical sympathetic nerve in dogs caused flushing of the mucous membrane of the mouth and gums. But, as Gaskell points out, it is very probable that the results were due to the stimulation of secretory fibres to glands, which exist in numbers in these regions. Their metabolites would explain the dilatation. At all events, this possibility has not been disproved.

After ergotoxin, Dale (1906) found that stimulation of the abdominal sympathetic chain caused vaso-dilatation in the hind-leg, and that of the splanchnic, vaso-dilatation in the intestine. Since this drug paralyzes vaso-constrictors and leaves dilators intact, the natural explanation of the result is that the nerves in question contained both kinds of fibres and that the dilator effect was masked until the opposing fibres were put out of action. The possibility of reversal of excitation to inhibition by ergotoxin has not, however, been definitely excluded. Further discussion of reversal phenomena with drugs will be found in Chapter V. Here, the reader is reminded of the probability, suggested by various experimental evidence, that a process resulting in inhibition can be changed into an excitation, or vice versa, by certain procedures, apart from the effects on different kinds of nerves.

As regards the vaso-dilatation from the splanchnic, it will be discussed below in connection with Bradford's work on the kidney. The evidence for the actual existence of vaso-dilator fibres in the abdominal sympathetic is conflicting. After degeneration of the dorsal root fibres in the sciatic nerve, no vascular dilatation can be produced by stimulation of it. It was also found impossible to obtain any effect of this kind by stimulation of the abdominal sympathetic by any method, even four days after section

(Bayliss, 1902), although Dziedziul (1880, confirmed by Bowditch and Warren, 1886), found that the vaso-dilators of the sciatic were intact at this time, while the vaso-constrictors were degenerated. Gaskell (1916, p. 90) shows that the vaso-dilator nerves to muscle, if they exist, do not pass in the abdominal sympathetic; since it is only stimulation of the anterior roots of the sciatic plexus that will cause increased rate of blood flow through the leg muscles, and these roots are below the origin of the sympathetic fibres.

The vaso-dilatation in the submaxillary gland, held by some to indicate the presence of vaso-dilators in the cervical sympathetic, was shown above to be due to chemical action on the part of the metabolites produced by the secretory activity of the cells of the gland.

The action of adrenaline is closely linked with the question of the presence of vaso-dilator fibres in the sympathetic. There is no doubt that small doses of this substance, instead of causing the usual rise of blood pressure by stimulation of the sympathetic vaso-constrictors, give a fall of blood pressure (Figure 20). Opinions are at variance with regard to the cause of this fall. Thus, Cannon and Lyman (1913) show that the result of a given dose is of opposite sign according to the height of the blood pressure, that is, according to the degree of contraction already present in the arterial muscle. If this is great, the effect of adrenaline is to depress it, and vice versa. Hartman and Fraser (1917) hold that the effect is on the central nervous system, because section of the nerves of a limb reverses the dilator into a constrictor effect. But it is clearly impossible to exclude the effect of different degrees of contraction of the arterial muscle in such experiments. Hartman and Kilborn (1918) show that the dilator effect is absent in young kittens, in which adrenaline has a purely

constrictor effect in any dose that has any effect at all. As Cannon and Lyman point out (1913, p. 394), if the explanation is that the vaso-dilator endings are more sensitive to weak stimulation, the application of weak electrical stimuli to the splanchnic nerve should have a dilator effect. After tying off the supra-renal gland, they found, however, that stimulation of any kind that they applied to the nerve, if it had any action at all, was of a vaso-constrictor nature. It is possible, on the other hand, that the kind of stimulus used was an inadequate one for the mechanism concerned

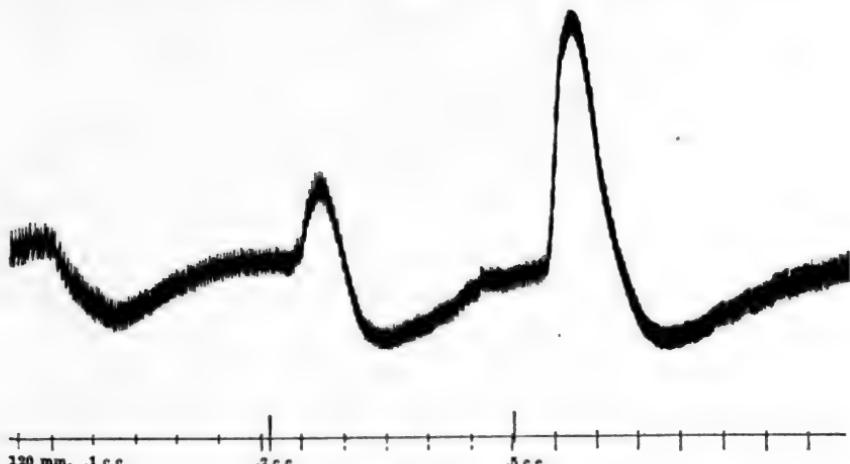


Figure 20.

Effect of Adrenaline on Blood Pressure.

Change from pure fall to fall and rise and then predominant rise with increasing doses (0.1, 0.2 and 0.5 c. c. of 1 in 10000 solution.

Time — half minutes.

(Cannon and Lyman, 1913, p. 383. Amer. Jl. Physiol.)

(see below). It is evident that any support that the vaso-dilator action of adrenaline gives to the hypothesis of the presence of vaso-dilator fibres in the sympathetic is of a very doubtful kind.

But, however this may be, the recent work of Dale and Richards (1918) shows that the dilator effect of ad-

renaline is almost certainly exerted on the capillaries. This question will be discussed in Chapter VI. If the capillaries were more sensitive than the arterioles, the effect on them might be present alone with small doses, while being over-powered by the arterial effect with larger doses. If we accept the view that the action of this substance is confined to the terminations of sympathetic nerves, we must postulate a sympathetic innervation of the capillaries. But caution should be exercised in making a dogmatic statement that adrenaline acts on no other structure than the myoneural junctions of the sympathetic system. Dale and Richards are inclined to think that the action on the capillaries is independent of the sympathomimetic action of the drug. They were also able to exclude definitely any central stimulation of dilators as an explanation of the depressor action.

There remain to be mentioned the experiments of Bradford (1889), who found vascular dilatation in the kidney to result from slow rates of stimuli applied to the splanchnic nerve or to certain mixed nerve roots. There are two circumstances, unknown at the time of these experiments, that suggest an interpretation without the need of assuming the presence of sympathetic vaso-dilators in the splanchnics. In the first place, the innervation of the suprarenals by the splanchnic would produce a small discharge of adrenaline, small enough to have a vaso-dilator dose, as Cannon and Lyman found (1913, p. 377) (see Figure 21).

Further, the possibility of antidromic effects from sensory fibres was not excluded in Bradford's experiments, since the posterior root fibres were stimulated along with those of the anterior root.

*Antidromic Vaso-Dilatation.* The remarkable nature of the vaso-dilator supply to certain parts of the body has been referred to above. The dorsal nerve roots concerned

are, as would be expected, those which contain the sensory fibres from any particular region and the effect is proportional to the size of the roots. Thus, dilatation of the hind-leg is obtained from the roots forming the sciatic plexus, that is, the 5<sup>th</sup>, 6<sup>th</sup> and 7<sup>th</sup> lumbar and 1<sup>st</sup> and 2<sup>nd</sup> sacral, greatest from that root which is the largest in any particular case.

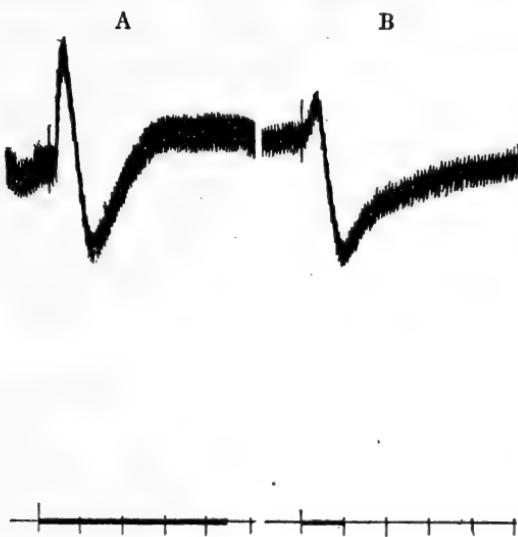


Figure 21.

Fall of Blood Pressure from Stimulation of Splanchnic Nerves.

- A Stimulation of left nerve (Direct effect on vessels plus that of secretion of adrenaline).
- B Stimulation of the same after tying arteries of the splanchnic area (Effect of secretion of adrenaline alone).

(Cannon and Lyman, 1913, p. 377. Amer. Jl. Physiol.)

It remains to mention the suggestions that have been made to explain the way in which it is produced. In my first paper on the subject (1901, p. 196), I pointed out that one possibility might be that the dorsal root fibres divide near their peripheral terminations, one branch supplying the sensory end-organ in skin, muscle, etc., while the other

ends as an efferent inhibitory end-organ on the muscular coat of the arterioles. Thus an impulse travelling in the antidiromic direction would show itself peripherally by its action on the latter only. It will be clear that a consequence of this arrangement, which is similar in some ways to that involved in Langley's "axon-reflex", would be that a stimulus to the sensory end-organ on one branch would pass to the arteriole on the other branch, in addition to being transmitted to the central nervous system. Ninian Bruce (1910) advocated a similar view, producing experimental evidence in its favour. A curious fact had been noticed by Spiess (1906) with regard to the vaso-dilatation induced by the application of oil of mustard to the skin. This effect is absent if the sensory endings are paralyzed by cocaine and it was thought by Spiess to be due to a reflex from the spinal cord to vaso-dilator nerves. Bruce, however, showed that the effect of oil of mustard is still present if the nerve trunks had been recently severed from the cord. Therefore, it could not be a spinal reflex. If, on the other hand, the nerve fibres were allowed to degenerate down to the periphery, oil of mustard failed to produce its effects. This result appears to be sufficient evidence that the vaso-dilatation is brought about by impulses from skin receptors, these impulses passing back from the nerve fibres by branches distributed to the inhibitory terminations in the arterioles. It seems desirable, nevertheless, that the experiments should be repeated.

If the capillaries are supplied with nerves, it is possible that some of the anomalies of the antidiromic effect might be explained by the passage of these fibres to the capillaries by way of the dorsal roots. This suggestion was made by Starling, while Krogh (1919, 2) brings some evidence bearing on the question. He was able to stimulate points on a capillary of the frog's tongue by local application of a pointed

glass rod, thus causing dilatation. If the nerves were intact, such local dilatation spread to more or less distant points in the capillary. Whereas, if the nerves to the tongue had been divided and allowed to degenerate, local dilatation limited to the point stimulated was the only effect. This investigator attributes the spreading to an axon-reflex in the sensory fibres. The spreading of the effect was also prevented by the application of cocaine. Doi (1920) finds that stimulation of the dorsal roots in the frog causes dilatation both in the arterioles and in the capillaries of the leg.

#### *AFFERENT NERVES FROM BLOOD VESSELS.*

It has been known since the work of Cyon and Ludwig (1866) that the stimulation of a certain afferent nerve, supposed to come from the heart, gives rise to reflex cardiac inhibition and vascular dilatation. It was hence called the *depressor nerve*. Its effects will be discussed under vascular reflexes below, but it may be mentioned here that it was shown subsequently that its main origin is from the arch of the aorta. It would therefore seem not unlikely that similar reflexes might be obtained from more peripheral vessels. Dogiel (1898) made microscopic preparations showing the presence of sensory endings in blood vessels (see Figure 3, p. 4 above). Latschenberger and Deahna (1876) put forward a theory of regulation of blood pressure according to which a rise of pressure in an artery causes the stimulation of depressor endings. The normal pressure is accordingly always giving rise to depressor impulses, so that, if the pressure falls, there is a decrease in these depressor impulsus and a resulting rise in the general arterial pressure. The experimental evidence is that, if the femoral artery is clamped, there is a rise of arterial pressure

greater than is to be accounted for by the mechanical effect of cutting out this area. If the clamp is removed, the pressure in the general circulation falls. The complications introduced by asphyxial conditions in the leg make the interpretation of these results rather doubtful. Reid Hunt (1895) confirmed the facts, pointing out that the mechanical effect of clamping is immediate, whereas there is a delay of a minute and a half in the appearance of the, presumably reflex, rise, which, moreover, does not appear if the nerves had been cut. Reid Hunt, however, is inclined to accept the interpretation given by Zuntz, namely, that there is an asphyxial stimulation of ordinary sensory nerves in the limb deprived of its blood supply. The fall on removal of the clamp was doubtless due to chemical products in the asphyxiated tissues.

Heger (1887) obtained a rise of blood pressure on injecting irritant substances, nicotine and silver nitrate, into peripheral arteries. It is difficult here to exclude action on nerve endings outside the blood vessels. The fact was confirmed by Pagano (1900), Spalitta and Consiglio (1896) and Delezenne (1897), who found that a rise of pressure in the artery of an artificially perfused paw, connected with the rest of the animal only by nerves, brought about a reflex rise in the aortic pressure. According to Siciliano (1900), the slight rise of pressure produced when the carotids are clamped is due to the removal of the depressor impulses previously sent out by the stretching of their walls.

It will be seen that the problem is a difficult one and that the experimental results are somewhat equivocal. Further investigation is needed. It may be that the reflex fall of pressure obtained under special circumstances from ordinary sensory nerves is due to the stimulation of depressor fibres arising from blood vessels and running in these nerves. Reflexes of this kind will be discussed in Chapter IV.

## CHAPTER III.

### *EFFECTS OF STIMULATION OF VASO-MOTOR NERVES.*

Since the methods of investigation of vaso-motor changes depend on the nature of the effects produced, it is necessary to devote a few pages to the consideration of these latter.

In general, a distinction may be made between the effects on the general blood pressure and those on the circulation in individual organs or tissues. If the arterioles of a particular region constrict, the peripheral resistance rises so that, with a given rate and force of the heart beat, the aortic pressure rises, while the magnitude of this rise depends on the extent of the area affected. Similarly, a dilatation of arterioles has the opposite effect. If we know that the heart beat has remained constant and that no loss of blood from the circulation has occurred, we may conclude that a rise of aortic pressure means that peripheral vaso-constriction has taken place and that a fall in this pressure means that vaso-dilatation has occurred.

The effects on a given region of constriction or dilatation of the arterioles supplying it are those implied by a reduction or increase of the blood supply, respectively; provided that the rise or fall of general arterial pressure does not counteract the local effect. As a rule, this latter circumstance does not interfere with the detection of the

effects produced by direct stimulation of the nerves supplying an organ, but it has to be taken into account in the case of wide-spread reflexes. Thus, it may happen that the reflex vaso-dilatation in the paw may be over-powered, so far as the local effects of increased blood supply are concerned, by the large fall of pressure due to vaso-dilatation in the remainder of the body. If we greatly decrease the volume of the latter by evisceration, the general fall of pressure is reduced and the dilatation in the paw is allowed to show itself.

Methods have been devised by which a rise or fall in arterial pressure is compensated automatically by allowing blood to escape or run in. A vessel of hirudinized or defibrinated blood from the animal used is connected to an artery and maintained at a constant pressure by a mercury reservoir (Bayliss, 1908). Such methods are successful when the change of pressure is not rapid. Otherwise, the rate of escape or inflow is insufficiently prompt to do more than compensate partially. In all probability, 6 or 7 per cent. gum. arabic in 0.9 per cent sodium chloride would serve equally with blood, and, in the case of a small animal, the initial removal of blood might be deleterious. It should always be replaced by an equal volume of gum-saline injected into the veins. The most appropriate procedure would be to remove a volume of blood, not more than about one-third of that in the circulation, replace this by gum-saline, and use in the compensator the blood removed, after defibrination and dilution with gum-saline to make it equivalent to the mixture present in the body. It should be tested whether the fluid which runs in has any direct action of the blood vessels, as done in Figure 22.

The effects of a change in the blood supply of an organ, so far as they are readily detected by brief observation, are changes in depth of red colour, in the rate

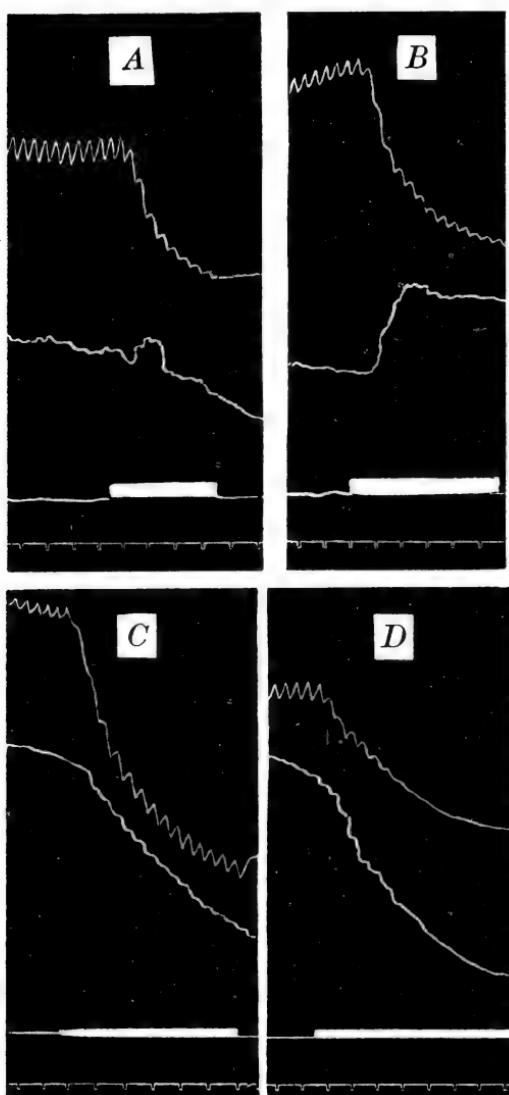


Figure 22.

## Use of Mercury Compensator.

Upper trace in each — arterial pressure.

Lower trace — Volume of hind limb.

Decerebrate cat, curarized. Stimulation of central end of right vagus.

*A* Without compensator.

*B* With compensator.

*C* After section of nerves to limb, without compensator.

*D* " " " " " " with " "

of outflow from the veins, in the size of the organ and, in some cases, in its temperature. We may consider each of these in turn.

*Changes in Colour.* Although this method has its advantages in requiring no interference with the organ, except exposure in some cases, it is clearly only available when the changes are fairly large and the colour of the tissues does not interfere. Failure to observe a change in colour does not disprove the presence of vascular effects. We shall see later that valuable information as to the state of the capillaries can be obtained by inspection.

*Venous Outflow.* This method usually requires the blood to be made non-coagulable by hirudin or defibrination and frequently, as in the case of the sub-maxillary gland, a somewhat tiresome ligature of collateral veins. The necessity of hirudin might be avoided by the use of a vein canula on the principle of that used by Hedon (1910) for crossed circulation. It consists of a piece of vein drawn through a metal tube and turned over at the ends. Thus, the blood is only brought into contact with vascular endothelium. If the rate of flow is indicated by a drop recorder, as is convenient for graphic registration, it is assumed that the drops are of equal volume. This would only be the case if the surface tension and density of the blood remained unaltered. In the investigation of small changes in rate, this factor might need to be controlled.

An objection to the method in general is the loss of blood that it entails. If hirudin be used, the blood can be returned to the circulation at frequent intervals. The volume might be made up by the addition of gum-saline (see below, p. 145). At the same time, it is sometimes the only method available. It has the advantage over the plethysmographic method of avoiding possible errors from change in general venous pressure and of differentiating to some extent

between action on arterioles and on capillaries. Figure 23 shows, by comparison of B and C, that although histamine causes a greater increase in volume than acetyl-choline does, the increase in venous outflow is greater in the second case. Thus the increase in volume is not necessarily in proportion to the increased blood flow.

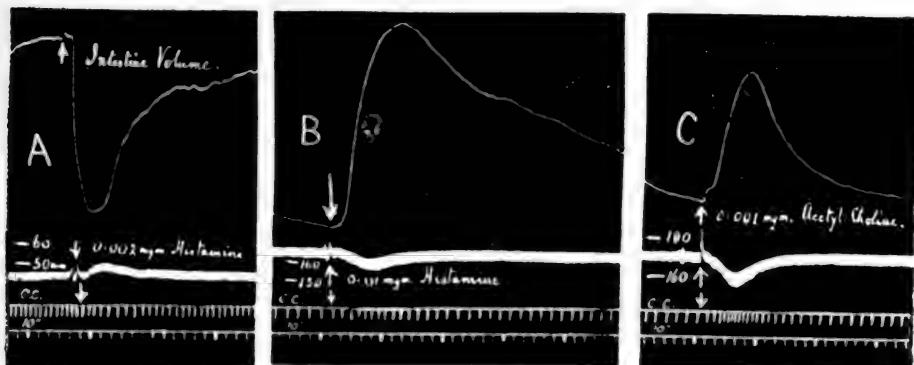


Figure 23.

Actions of Acetyl-choline and of Histamine.

Perfusion of intestinal loop. Volume, perfusion pressure, venous outflow and time in 10 sec. in order from above downwards.

Perfused with hirudinized blood, containing a trace of adrenaline.

(Dale and Richards.)

*Change in Volume.* Any dilatation or constriction of arterioles in a region of the body is obviously associated with an alteration in volume of the region. This is exaggerated by the resulting passive distension or emptying of the capillaries, provided that the outflow by the veins is not such as to keep the capillaries at their normal volume. Since evidence was brought by Starling and myself (1894) that the capillary pressure is more directly related to that in the veins than to that in the arteries, the state of distension of the capillaries will depend rather on the indirect effect of the arterial pressure on the general venous pressure (see also Krogh, 1920).

The method of investigation of changes in volume of organs is known generally as the *plethysmographic* method and has been of great service in researches on vaso-motor mechanisms. The use of the air-plethysmograph will be found in the paper by Schafer and Moore (1896) and, as applied to the intestine, by Edmunds (1897). The best method for use with the limbs is described by Dale and Richards (1918).

If there is simultaneously a direct effect on the capillaries, the plethysmographic method cannot distinguish it from a similar one on the arterioles, while if the effect is of an opposite nature on the two, there may be either increase or decrease of volume.

Caution has also to be exercised in the interpretation of plethysmographic curves when the effect is accompanied by a change in general arterial pressure, as in vaso-motor reflexes. If a decrease in volume of an organ is associated with a rise in general arterial pressure, it is obvious that a vaso-constriction must be present in the organ, because the effect of the rise of pressure would be to distend it. Similarly, when increase in volume coincides with a fall in arterial pressure, there must be local vaso-dilatation. But if there is increase in volume along with rise of arterial pressure, no conclusion can be drawn. There may be either vaso-constriction of a slight degree overpowered by the raised arterial pressure, there may be no local effect or there may be vaso-dilatation. And correspondingly for the case of decrease of volume.

When vascular reflexes to the limbs are under observation, the elimination of a large part of the remaining vascular bed by evisceration is frequently of service in diminishing the passive effects of rise and fall of pressure in the arterial system generally.

*Temperature.* In the case of the skin, which is normally at a lower temperature than the blood, an arterial dilatation produces a rise of temperature. On the other hand, a capillary dilatation does not of necessity raise the temperature, although there is hyperaemia. As will be seen later, such phenomena are of significance with respect to the reactions of the capillaries.

*Cross-Circulation and Artificial Perfusion.* In order to avoid the various passive effects of changes in the general blood pressure, the method of cross-circulation is sometimes used. Some particular organ is fed from the circulation of another animal, while still remaining in nervous connection with the body of that animal to which it belongs. Artificial perfusion with blood or some appropriate liquid may also be employed. With reference to the properties required in this fluid, the author's article on gum acacia (1920, 2) may be consulted. Figure 62 below is an illustration of the former method and Figure 23 of the latter.

### INFLAMMATION.

It will probably be noticed how the classical signs of inflammation, heat, redness and swelling, are evidence of arterial dilatation. As to the fourth sign, pain, the intervention of the dorsal root fibres in antidromic vaso-dilatation is of interest.

The formation of blisters raises the question whether vascular dilatation in itself is sufficient to have this effect. If it is true that cocaine or degeneration of the dorsal root fibres prevents the action of oil of mustard, it would seem that the blistering effect must be due to stimulation of vaso-dilators as such. The localization by Head and Campbell (1900) of the lesion in *herpes zoster* in the cells of the dorsal root ganglion points in the same direction.

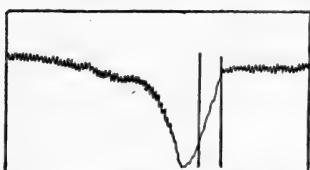
*BALANCE OF EFFECTS.*

Since Pavlov showed, as mentioned above, that the excitatory and inhibitory nerves act directly on the smooth muscle fibres, it is to be expected that by simultaneous stimulation of vaso-constrictor and vaso-dilator nerves mutual antagonism may result in absence of effect. Experiments of this kind on simultaneous stimulation of the *chorda tympani* and sympathetic supply to the submaxillary gland were made by Von Frey (1876) and by Asher (1909). It was found that, by appropriate choice of the relative strengths of the stimulation applied, balance could be obtained and the effect of either made to preponderate, according to which received the more powerful stimulus. Anrep and Cybulski (1884) made similar experiments on the tongue.

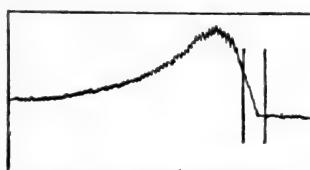
Experiments in which balance of opposite effects was obtained in reflexes are of course of a different nature, since the opposing influences are exerted on nerve cells, not directly on the arterial muscle. They will be described later.

The frequent presence of both vaso-dilators and vaso-constrictors in the same nerve trunk renders it difficult in such cases to show the existence of both, especially if there is a preponderance of either kind. The two kinds of fibres have, however, as a rule, a different optimal rate of incidence of energy for stimulation, so that the one kind may be excited by a strength of stimulus which is inadequate for the other, provided that the rate of incidence of the stimulus in the former case coincides with the resonance of the excitable structures more effectively than in the latter case (see Keith Lucas, 1906, 1, 2 and 3). Thus, stimulation of the peripheral end of the sciatic nerve by ordinary tetanizing induction shocks, which have a very

rapid time course, or rate of incidence of energy, always results in vaso-constriction. A series of snips with scissors almost as invariably gives dilatation from the same nerve. Weak induction shocks applied at a slow rate sometimes cause vaso-dilatation, as shown by Bowditch and Warren (1886); but in my hands this method has not shown itself reliable; probably the method of interruption of the primary circuit was different from that used by Bowditch and Warren. It might be supposed that the vaso-constriction produced by cold would favour the manifestation of vaso-dilator effects. But Bowditch and Warren were unable to detect



Nerve freshly divided.



Nerve 4 days degenerated.

Figure 24.

## Vaso-Motor Nerves of Leg.

On the left—plethysmographic curve on stimulation of freshly cut sciatic nerve.

On the right — effect four days after section of the nerve.

Each curve to be read from right to left. A fall means constriction, a rise, dilatation. (Bowditch and Warren, 1886, p. 444.)

any influence of this kind and I found myself that the antidromic dilatation was best seen if the leg was kept warm. Another property of the vaso-dilator nerves is that of less rapid degeneration after separation from their trophic centres than is that of the constrictor fibres. Thus, Bowditch and Warren found that the former had lost their excitability about the 7<sup>th</sup> day, the latter on the 4<sup>th</sup> day. Even on the second day, the vaso-dilator effect is much more marked than the vaso-constrictor one (Figure 24). According to experiments made by Head and myself (unpublished), the dilators of the radial nerve *regenerate* earlier than the con-

strictors. These dilators being probably protopathic sensory fibres, this result would be expected from the work of Head and Rivers (1908). The sympathetic constrictors do not regenerate until a much later date.

Howell, Budgett and Leonard (1894) found that the vaso-constrictors in the sciatic nerve could be more easily blocked than the dilators by cooling the nerve peripherally to the point of stimulation. The constrictors were completely blocked at  $2^{\circ}$  or  $3^{\circ}$  C., whereas there was still a slight degree of vaso-dilatation on stimulation.

Further work on the lines of Keith Lucas' researches is desirable.

## CHAPTER IV. *VASO-MOTOR REFLEXES.*

The fact that reflexes to vaso-motor nerves are readily evoked by stimulation of various afferent nerves, and that these may be either of the nature of vaso-dilatation or vaso-constriction, was referred to incidentally in speaking of afferent nerves from blood vessels. Since the former show themselves in a fall of arterial pressure, they are often called "depressor" reflexes; the latter, associated with a rise in arterial pressure, are then known as "pressor" reflexes. There must be, accordingly, some region or regions in the central nervous system serving as centres for these reflexes.

### *VASO-MOTOR CENTRES.*

It was shown by Dittmar in 1873 that if the brain stem is gradually sliced away from above downwards, no effect on the blood pressure is observed until the middle of the pons is reached. Progressive slices then cause a greater and greater fall until the upper part of the bulb is reached. From this point on, no further effect is produced. This behaviour is usually held to indicate a centre from which vaso-constrictor impulses are normally proceeding.

No further definite advance was made until the experiments of Ranson and Billingsley in 1916. Various evidence had accumulated showing that there is also a

centre for vaso-dilator nerves and these authors investigated the question by exploration of the floor of the fourth ventricle in the cat, using weak localized stimuli by the unipolar method. They found that there were two points which uniformly responded by changes in the blood pres-

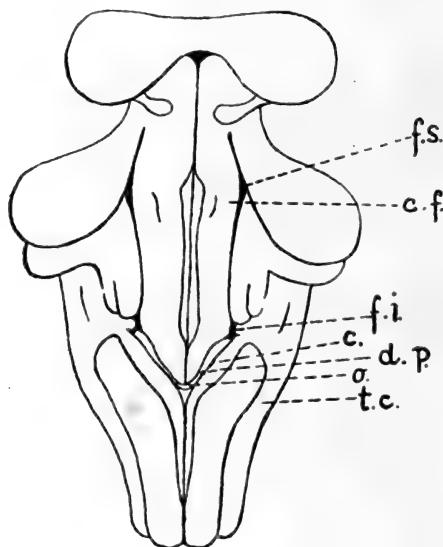


Figure 25.

Diagram of the Floor of the Fourth Ventricle in the Cat.

*f. s.* Fovea superior.

*d. p.* Depressor point.

*c. f.* Colliculuc facialis.

*o.* Obex.

*f. i.* Fovea inferior.

*t. c.* Tuberculum cinereum.

*c.* Clava.

(Ranson and Billingsley, 1916, p. 86. Amer. Jl. Physiol.)

sure, whereas other points gave no results with similar strengths of stimuli, with the exception of the facial colliculus, which sometimes gave a rise of pressure, probably due to afferent fibres to the other points. The point marked *d. p.* in Figure 25 gave always a fall of blood pressure (Figure 26). It is in the extreme posterior part of the fourth ventricle, just lateral to the obex. The other point

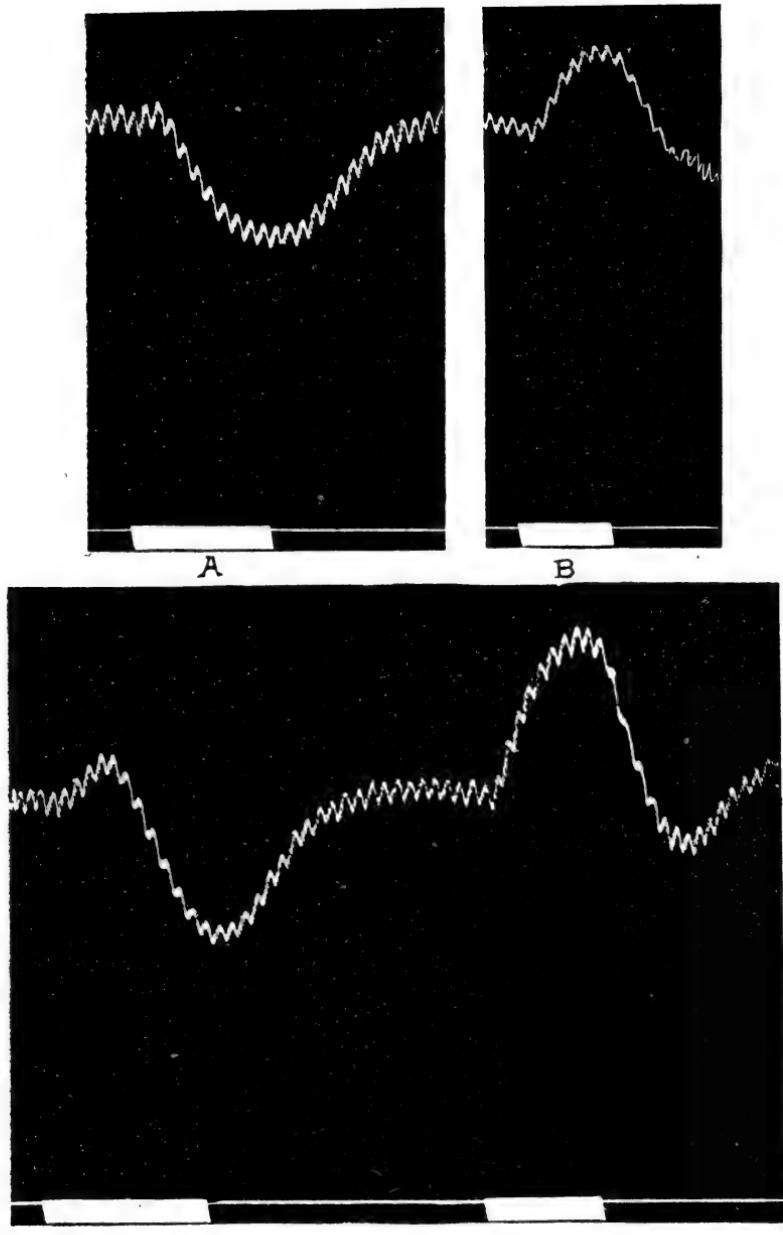


Figure 26.

Stimulation of the Fourth Ventricle.

A Fall of blood pressure from the depressor point.

B Rise of pressure from the pressor point.

Cat. Vagi cut. Ether and Curare. (Ranson and Billingsley, 1916, p. 88.)

[Amer. Jl. Physiol.]

is the apex of the ala cinerea or the fovea inferior and gives a rise in blood pressure. The two points are only three millimeters apart, so that it was only possible to use very weak stimuli.

It may be that these are merely afferent tracts in connection with the centres, but their very localized position and response to stimuli that have no effect when applied to other regions suggest that they are definite centres.

These centres in the bulb are, so far as present evidence goes, the supreme coordinating centres. When vaso-motor effects are obtained from higher parts of the brain, it seems that the stimulation of afferent fibres to the bulbar centres is responsible.

The heat centres in the corpus striatum are in intimate relation with the vaso-motor centres. Thus, when the temperature of the blood rises, there is vaso-dilatation in the skin (see Barbour, 1912).

As in the case of reflexes generally, there are subordinate relay centres in the spinal cord, and there are also cell stations in the ganglia of the sympathetic chain and more peripherally situated plexuses in the case of the vaso-constrictor nerves. The details of these have been worked out by Langley and his coadjutors (1900). The peripheral cell stations of the vaso-dilator nerves are in the immediate neighbourhood of the structures supplied. None of the ganglia situated more peripherally than the spinal cord has been shown to be capable of reflex action. Certain phenomena of apparently reflex nature were shown by Langley and Anderson (1894) to be due to branching fibres ("axon-reflex").

The vaso-motor centres in the spinal cord are very inactive for some time after separation from the bulb, owing to "spinal shock". Only a slight rise of pressure can be obtained by stimulation of the central end of the

sciatic nerve, a somewhat more marked one from the central end of the splanchnic (Figure 27). In the course of some days or weeks, the cord recovers its excitability and a

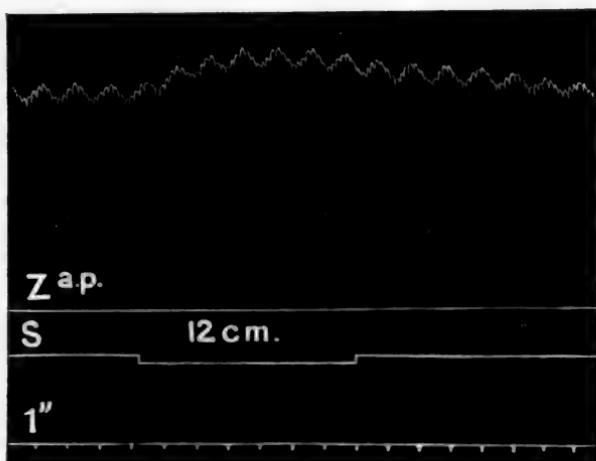


Figure 27.

Effect of Stimulation of the Central End of the Splanchnic Nerve in the Spinal Cat.  
(B. C. V. Mellé and J. L. Shipley.)

Z. a. p. zero of arterial pressure.

S Signal of stimulation.

Time in 1".

(Sherrington's "Mammalian Physiology" [Clarendon Press] 1919, p. 43.)

large pressor effect is obtained even from a digital nerve (Sherrington, 1906, p. 242) (Figure 28 p. 58).

After a small dose of strychnine, a good result can be obtained from the sciatic nerve an hour or two after section of the cord. Whether this is due to removal of block at the synapses or to an increase of excitability of the centres is a matter of dispute (Langley, 1919).

The spinal centres are excited by the chemical changes of *asphyxia* in the cells (Sherrington, 1909). They are not so easily excited by carbon dioxide as the bulbar centres are, and, according to Mathison (1910, 1911), the response to deprivation of oxygen, which has a longer latency than

that to carbon dioxide, is due to the production of fixed acid in the centres themselves. This is sudden and occurs at the point when the cell mechanisms are beginning to be disorganized.

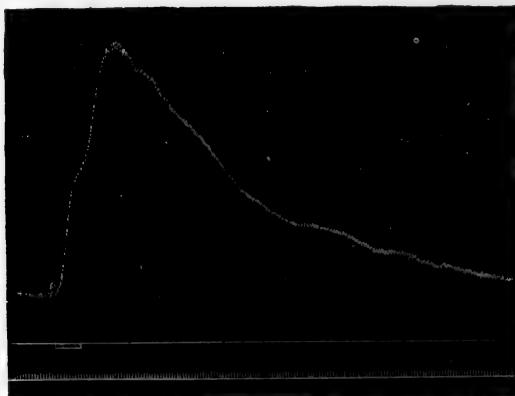


Figure 28.

Spinal Vaso-constrictor Reflex.

Dog. 300 days after spinal transection at 8<sup>th</sup> cervical.

Stimulation of central end of a digital nerve of the hind limb at the signal mark on second line from bottom. Arterial pressure rises from 90 mm. Hg. to 208 mm. Hg. Time in 2 secs.

(Sherrington's *The Integrative Action of the Nervous System* 1906, p. 242.  
Yale University Press.)

The sensitivity of the vaso-motor centres to increased hydrogenion concentration in the blood renders it difficult to decide whether they are automatic, in the sense of sending continuous impulses along the efferent nerves, apart from reflex stimulation. Under usual conditions, it is easy to show the existence of "tonic" vaso-constrictor impulses, less easy to detect tone of the vaso-dilator centre. These states may well be due to receipt of afferent impulses and will come up for further consideration later.

The rhythmic waves in the arterial pressure known as *Traube-Hering* curves indicate an automatic activity of the

vaso-motor centres. The mode of genesis is shown by Figure 29 to be a periodic peripheral constriction and dilatation.

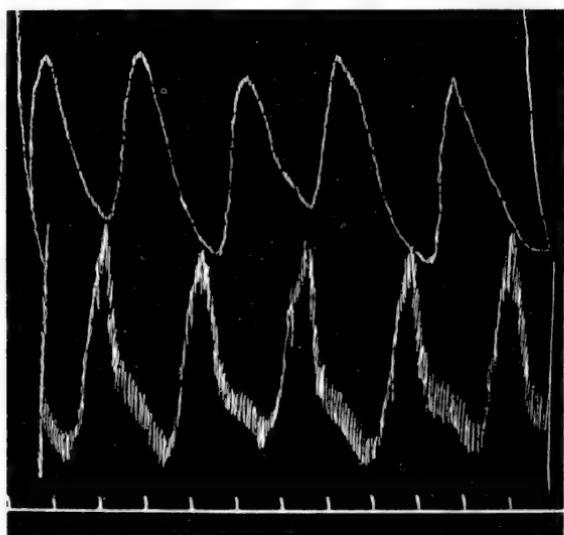


Figure 29.

Traube Waves.

Upper tracing — volume of the leg of a dog. Descent = contraction.

Lower tracing — arterial pressure. Zero below the figure.

Time in 10".

(Bayliss and Bradford.

The fact that an artificially perfused organ, remaining in connection with the nervous system, reacts to haemorrhage by vaso-constriction, as shown by Pilcher and Sollmann (1914) and confirmed by Bainbridge and myself, might be due either to anaemic stimulation of the constrictor centre, or to removal of tonic depressor impulses, or again to a direct sensibility of the centre to changes in blood pressure. The first possibility, if interpreted in the sense of defective blood supply, seems improbable on account of the rapid onset and the comparatively small fall of pressure which suffices to evoke the response. The second pos-

sibility has not, so far as I am aware, been tested by section of the depressor nerves, but seems excluded, as a complete



Figure 30.  
Effect of Gravity on the Monkey.

Blood pressure. Vagi cut. Rotated around axis of carotid artery.

A Vertical, feet down.      B Horizontal.      C Vertical, feet up.      D Horizontal.

Note effect at B, vessels still constricted.

(L. Hill, 1895.)

explanation, by the experiments of L. Hill (1895), in which the effect of gravity on the abdominal circulation was shown to be corrected by vaso-constriction, especially in those animals which habitually assume an upright posture. In the experiment of Fig. 30, the vagi, presumably including the depressor fibres, were cut and the animal was rotated around an axis passing through the insertion of the canula in the carotid artery. It does not seem likely that the effects here were due to stimulation of depressor endings in the aorta, but it is difficult to exclude stimulation of other peripheral receptors, such as the Pacinian bodies in the mesentery of the cat. If these are excluded, sensibility of the centres to rise and fall

of pressure in their arteries must be assumed, as has indeed been done.

Pilcher and Sollman also found that transfusion of blood was associated with vaso-dilatation. The remarks made above apply to this case also, *mutatis mutandis*. The question of the direct effect of blood pressure on the centres will be discussed again below, but it requires further investigation.

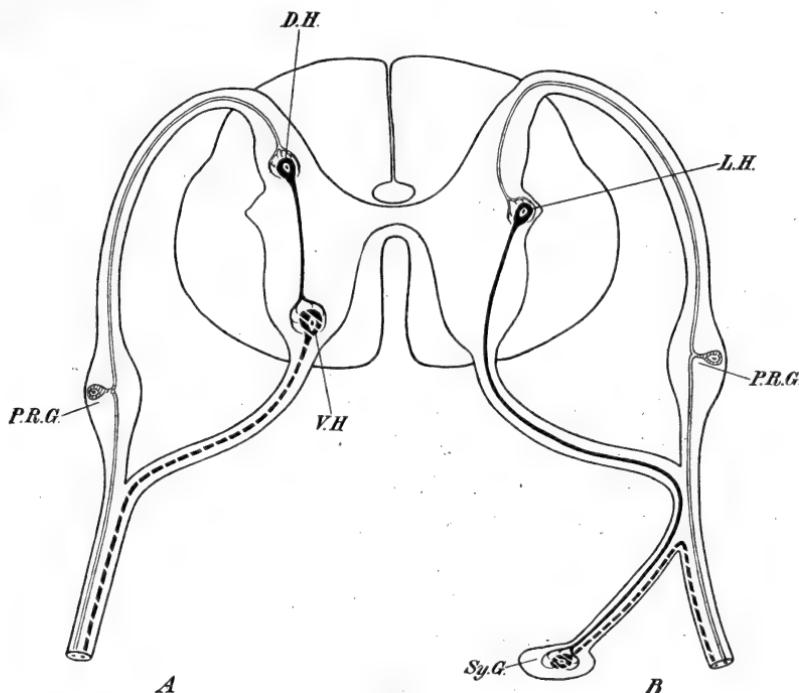


Figure 31.

Reflex Paths in the Cord.

White-receptor neurones.

Black-connecting neurones.

Dotted-excitatory neurones.

A. Voluntary system.

B. Involuntary system.

P. R. G. dorsal root ganglion.

D. H. dorsal horn.

L. H. lateral horn.

V. H. ventral horn.

Sy. G. sympathetic ganglion.

(Gaskell, 1916, p. 9.)

The "centres" of the sympathetic system in the spinal cord and the nature of the white rami and the ganglia

will be made clear by Figure 31. The situation of the cells of origin of the sympathetic in the lateral horn was advocated by Gaskell in 1885 and confirmed by Anderson (see Gaskell, 1916, p. 132), who found that section of the cervical sympathetic in young kittens caused a marked failure of the growth of cells in the lateral horn in the upper thoracic region. The view is now generally accepted.

#### *VASO-MOTOR REFLEXES.*

The control by the central nervous system of the state of contraction of the arterioles may be said to serve two main purposes. A generalized vaso-constriction raises the aortic pressure and affords a better supply of blood to organs whose arterioles are not narrowed, because they are poorly, or not at all, supplied with vaso-constrictor nerves, such as the coronary vessels of the heart and the vessels of the brain. The failure of constriction in a given part may also be on account of a dilatation due to a coordinated (Lovén) reflex, as will be seen later. It may be said that the heart and the brain are of such supreme importance and so sensitive to deficient supply of blood that the rest of the body has to be subservient to them, since it must be remembered that, although vaso-constriction raises the feeding pressure to an organ whose vessels are constricted, the net result is usually a decrease of supply to that organ itself. The raised pressure is more than counterbalanced by the constriction of the channels. Even a small degree of narrowing has a marked effect on the flow.

The chief use of a generalized dilatation seems to be to relieve the heart from the effort required to pump the blood against too high an arterial pressure. Such a raised pressure may be produced by actions which compress large venous reservoirs.

In considering the results of such wide-spread vaso-motor effects, the factor of *capacity* of the vascular system must be kept in view. Stress was laid on this factor by Ludwig and his school. Starling and myself (1894) devoted some work to its elucidation. Although it may be true that the great veins can accommodate varying quantities

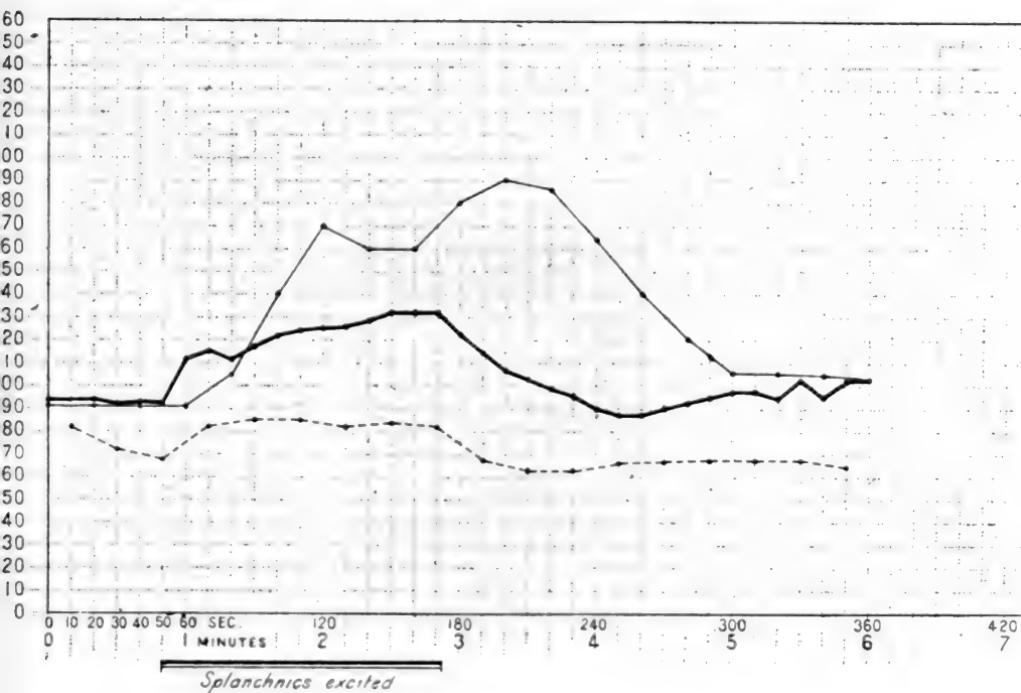


Figure 32.

Effect of Splanchnic Stimulation on Arterial and Venous Pressures.

Thick line — arterial pressure.      Thin line — pressure in portal vein.  
Thin broken line — pressure in inf. vena cava.

Arterial pressure in mm of mercury, venous pressure in mm of 25 per cent. magnesium sulphate solution.      (Bayliss and Starling, 1894.)

of blood without much rise in internal pressure, owing to the thinness of their walls, it is clear that if the amount of blood in actual circulation is diminished by dilatation of arterioles and capillaries, that supplied to the heart by

the veins is decreased and therefore that sent out in systole. The capacity factor tends to increase the effect of the decrease in peripheral resistance on the aortic pressure. Similarly, the effect of a general vaso-constriction is to increase the amount of blood in the heart and therefore in circulation. If, indeed, the result of arterial dilatation were to raise the venous pressure, as it would if the capacity factor were non-existent, the object of such dilatation would be to a large extent defeated, since the output of the heart would be increased and the aortic pressure so far raised as to annul in part the effect of the peripheral dilatation.

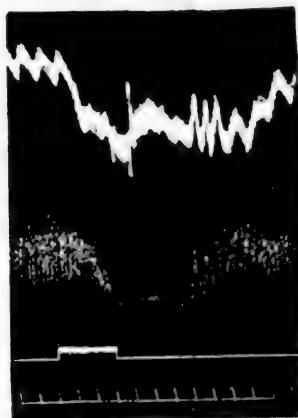


Figure 33.

Vena cava Pressure in the Cat on Depressor Stimulation.

Upper curve — arterial pressure. Zero 15 mm below signal.

Lower curve — pressure in central end of iliac vein, i. e. in inf. vena cava.

(Bayliss, 1902.)

In point of fact, Starling and I were able to show that, after section of the spinal cord, which causes general dilatation of arterioles, the vena cava pressure was unaltered, although, if the capacity factor is neglected, the increased blood flow through the body should have resulted in a rise. Again, stimulation of the splanchnic nerves raises

the vena cava pressure, instead of lowering it (Figure 32). The same thing happens in the first stage of asphyxia. Figure 33 shows that the effect of depressor stimulation is to lower both arterial and venous pressures. Occasionally, the fall of venous pressure is preceded by a rise, the effect of the increased blood flow before the capacity effect begins to show itself.

The second purpose for which control of arterioles is needed is to adjust the supply of blood to individual organs according to their needs.

#### *DEPRESSOR REFLEXES.*

*The Depressor Nerve.* For the object of analysis of vascular reflexes, the depressor reflexes may with advantage be taken first, and especially that one obtained from a particular nerve, which is a branch of the vagus. This "depressor" nerve is in some animals, as the rabbit, a separate nerve trunk and, so far as can be ascertained, it contains no other kind of fibres than those which give rise to a combined reflex, an inhibition of the heart and a generalized vascular dilatation. In some other animals, such as the dog and the cat, the fibres are carried as a rule in the main trunk of the vagus, mixed with fibres of other kinds. In the cat, however, it is usually possible to find conditions in which the depressor effect alone shows itself. In the dog, it is sometimes found that stimulation of the central end of the vagus may produce a fall of blood pressure, but the result cannot be obtained at will.

The depressor nerve was discovered by Cyon and Ludwig (1866), who showed that if the vagi were cut, the cardiac inhibitory effect was abolished, but not the fall of arterial pressure; so that there was a reflex to the blood vessels in addition.

The receptor endings of the depressor nerve were at that time supposed to be situated in the heart, but it was shown by Tschermak and Koster (1902) that the greater number are in the arch of the aorta.

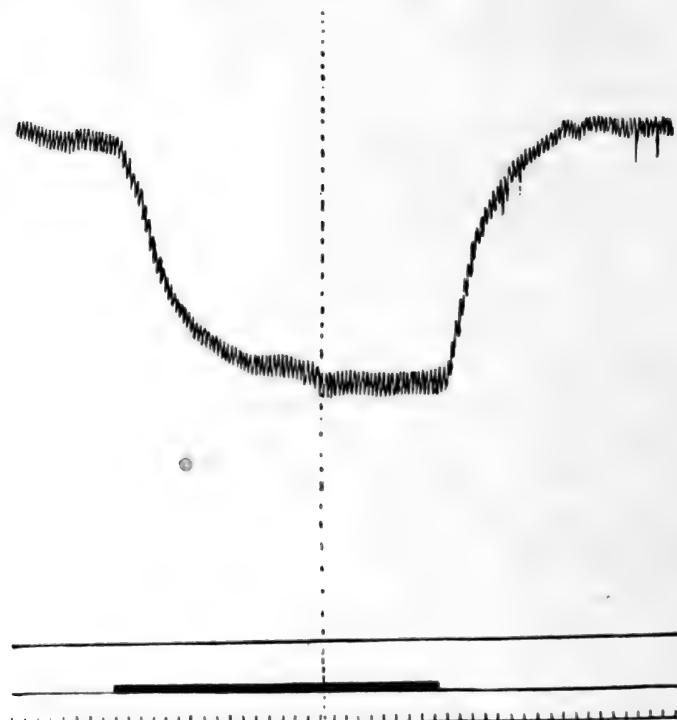


Figure 34.  
Depressor Nerve of the Rabbit.

The tracing shows the arterial pressure curve at the beginning and end of a period of stimulation lasting seventeen minutes. During the whole of this time the pressure remained at the level of the bottom of the curve.

Time in twelve-second intervals.

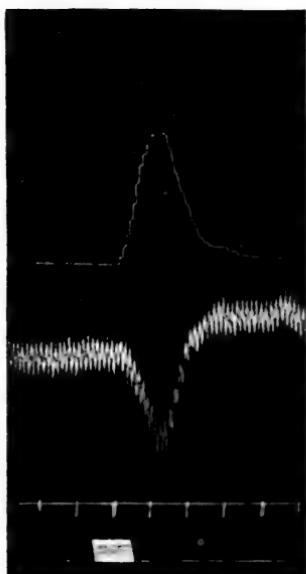
(Bayliss, 1893, Fig. 17.)

Figure 34 gives a typical depressor curve of blood pressure and curves 2 and 3 of Figure 35 show that the fall of pressure is actually due to vaso-dilatation.

We have seen above that the vaso-constrictor centre is normally in a state of tonic activity, sending impulses



1



2



3

Figure 35. Vaso-motor Reflexes.

Upper curves in each volume of intestine of cat. Fall indicates arterial constriction, and vice versa.

Lower curves — arterial pressure. Initial height, 90 mm. of mercury.

Each division of the scale represents 2 mm. of mercury.

Upper signal — time in 10". Lower signal — stimulation of nerves.

In 1, three stimulations of the central end of the median nerve.

In 2, a stimulation of the central end of the vagus (depressor).

Intestine dilates during the fall of pressure.

In 3, similar, longer, stimulation. Anaemia of the heart.

along the constrictor nerves. W. T. Porter holds that there is a vaso-tonic centre, distinct from the vaso-constrictor one (1910, 1915). In cats and rabbits, at regular intervals after injection of curare, the reflex effects are found to increase markedly, whereas the "tone", as indicated by the height of the arterial pressure, is unchanged. Porter and Turner (1915) showed that alcohol can abolish the reflex, leaving the tone unaffected. The interpretation of these results is not easy, but it is scarcely possible to regard it as established that the action of these drugs is exerted solely on the centre itself. They might also affect the synapses in such a way that their permeability was affected differently for natural and artificial rates of impulses. Moreover, the tonus of the centre might be caused by chemical agents, such as carbon dioxide, not by afferent stimulation. The natural tonus of the centre is demonstrated by the fact that if the sciatic nerve is cut, there is a long-lasting dilatation of the arterioles of the leg. On account of the presence also of vaso-dilator fibres in this nerve, which are probably stimulated by the act of section, a more convincing experiment is to divide the abdominal sympathetic, a proceeding which gives the same result (Figure 36).

This being the case, we see that if the stimulation of an afferent nerve had the effect of inhibiting the vaso-constrictor centre, a peripheral dilatation would be caused by removal of the tonic constrictor impulses. This was the way in which Cyon and Ludwig supposed the depressor nerve to act, and Figure 36 shows that it has this effect. Ostroumov (1876), however, on the basis of his experiments on reflex stimulation of vaso-dilator nerves, was inclined to believe that the depressor really excites the vaso-dilator centre, rather than that it inhibits the vaso-constrictor one. The results of some experiments that I made myself (1893) suggested that both processes were concerned. But it

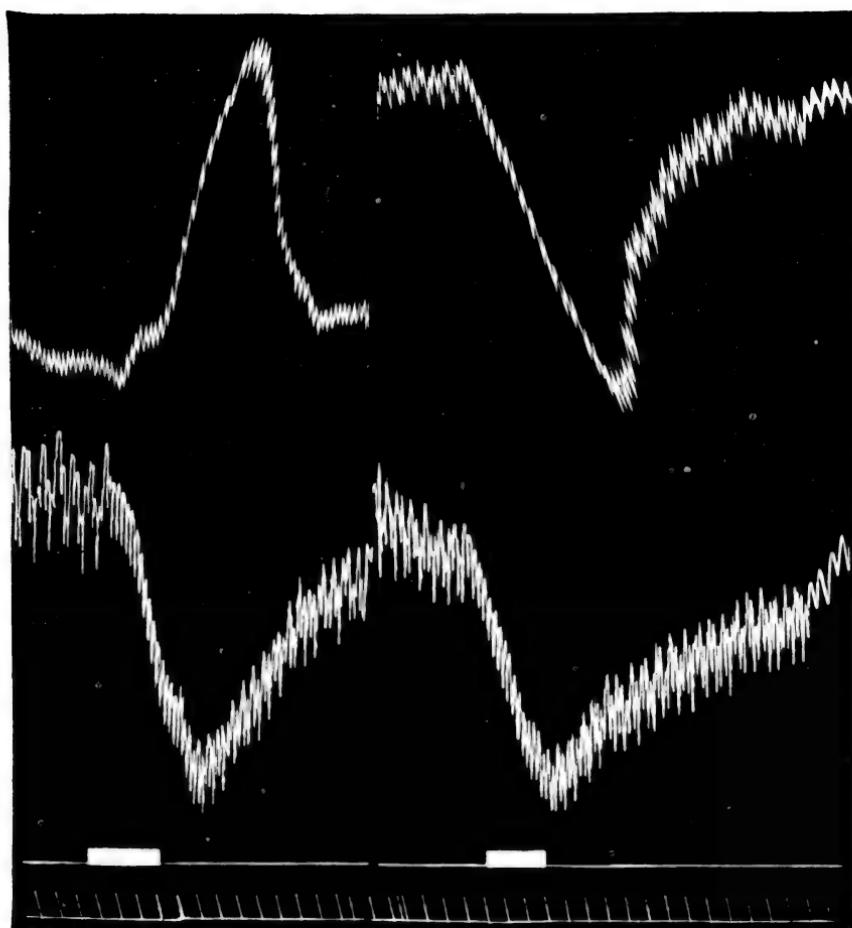


Figure 36.

## Depressor Reflex on the Hind Leg of the Dog.

Upper curves — leg volume. Rise — dilatation.

Lower curves — arterial pressure. Zero — 24 mm. below time signal.

Time in ten seconds.

First stimulation shows inhibition of tone in vaso-constrictor centre.

Between the two stimulations, the abdominal sympathetic was cut.

The tone of the centre was shown by the rise of the level of the limb tracing.

The second stimulation gives fall in blood pressure, but the leg follows the pressure passively instead of dilating.

The vaso-dilator nerves were cut, so that the result was due to inhibition of constrictor tone alone.

was not until after Sherrington's work on reciprocal innervation in reflexes to voluntary muscle that I took up the question again (1908). It has been shown above that in depressor reflexes there is an inhibition of the vaso-constrictor centre. It remains to find out whether the vaso-

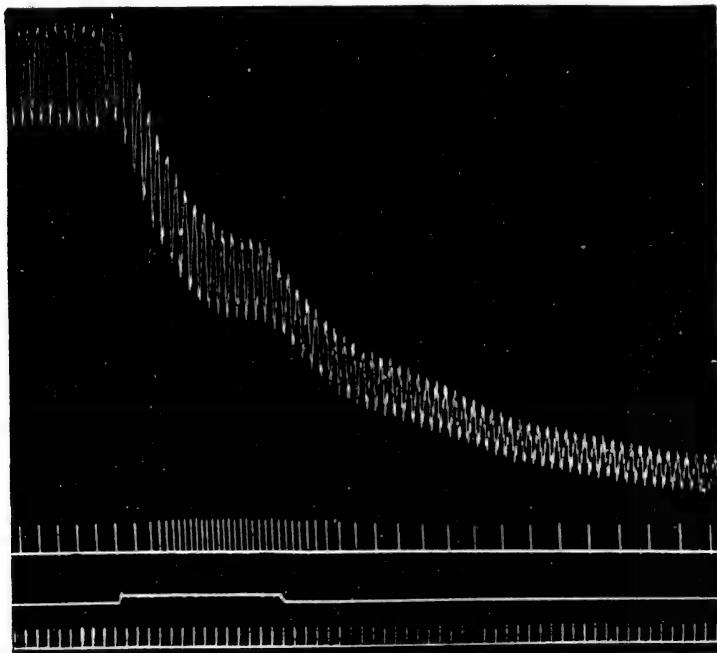


Figure 37.

Excitation of Vaso-dilators in Depressor Reflex.

Cat. Ce vical sympathetic cut. Chorda tympani only intact.

Upper trace — arterial pressure. Zero — 33 mm. below time signal.

First signal line from top — drops of blood from vein of submaxillary gland.

Second do. — stimulation of central end of opposite vagus

Third do. — time in two-second intervals.

(Bayliss, 1908, Fig. 1.)

dilator centre is simultaneously excited to activity. This can only be done by taking organs which can be deprived of their vaso-constrictor supply without interfering with their vaso-dilators. Such organs are few in number, practically only the submaxillary gland and the hind-legs.

Figures 37, 38 and 39 show that the vaso-dilator centre is actually excited. Confirmatory results have been obtained by Fofanow and Chalussov (1913) and by Martin and Mendenhall (1915).

The afferent fibres which cause the depressor reflex, then, obey a kind of reciprocal innervation, in that they excite the vaso-dilator centre and at the same time inhibit the tonic activity of the vaso-constrictor centre. Just as Sherrington showed that in reflex flexion of the knee, the centres for the flexors are excited, those for the extensors inhibited. The difference is that in the case of the smooth

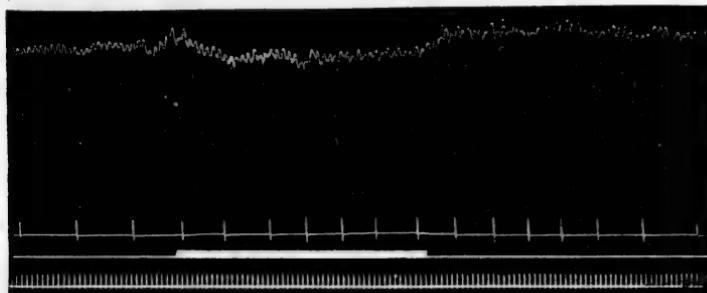


Figure 38.

Similar to Figure 37.

Rabbit. Depressor nerve stimulated.

Mercury compensator in use, so that the fall of blood pressure is small.

(Bayliss, 1908, Fig. 7.)

muscle of the arterioles, the effector muscle is one and the same, being naturally in a state of moderate contraction, which is in part due to the reception of excitor impulses from the vaso-constrictor centre, as long as their channels are intact, in part to its own inherent activity. It can be caused to relax either by removal of the constrictor impulses, or still further by the reception of vaso-dilator impulses which inhibit its natural "tone". It has indeed been shown by Goltz, Freusberg and Gergens (1875, p. 62) that

a greater degree of dilatation can be obtained by stimulation of vaso-dilator fibres than by merely cutting off constrictor impulses. The diagram of Figure 40 will serve to make the somewhat complex arrangement more intelligible.

Martin and Stiles (1914) describe two types of effect from the depressor nerve which suggest that the excitatory action on the dilator centre may be brought about by weaker stimulation than the inhibiting action on the constrictor centre. By gradually increasing the strength of

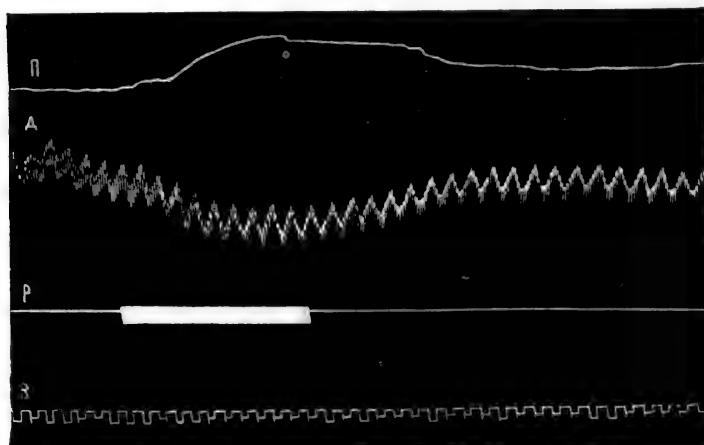


Figure 39.

Similar Experiment on the Hind Leg of the Dog.

Upper trace — volume of leg.

Lower trace — arterial pressure.

Upper signal — stimulation of central end vagus.

Lower do. — Time in seconds.

Abdominal sympathetic cut, so that the antidiromic dilators only were intact.

(Fofanov and Chalussov.)

the stimulus, a comparatively small effect is first obtained. This persists without significant increase until a larger effect is somewhat suddenly produced, which itself remains without further increase with continued rise in the strength of the stimulus. The authors interpret the former as due to

vaso-dilator excitation, the latter as inhibition of constrictor tone.

Sherrington (1906) calls attention to another aspect of the depressor reflex in which again reciprocal innervation

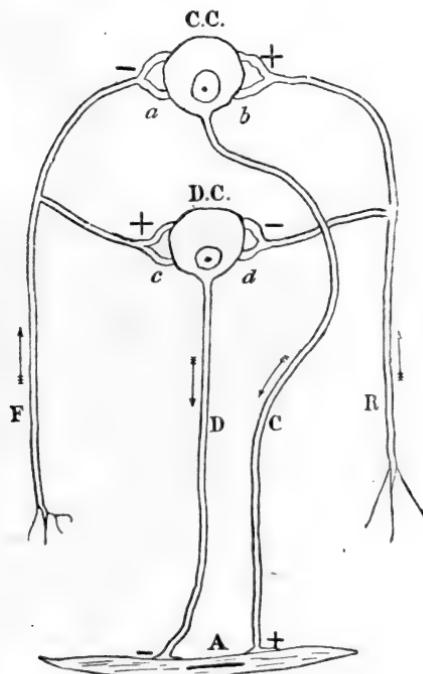


Figure 40.  
Diagram of Vaso-motor Reflexes.

- A.* Arteriole muscle.
- D.* Vaso-dilator fibre, inhibiting natural tonus of *A*.
- C.* Vaso-constrictor fibre, causing contraction of *A*.
- D. C.* and *C. C.* — Dilator and constrictor centres, resp.
- F.* Afferent depressor fibre, with two collaterals, one (—) inhibiting constrictor centre, the other (+) exciting the dilator centre.
- R.* Pressor fibre of ordinary sensory nerve, exciting *C. C.*, inhibiting *D. C.*
- a, b, c, d.* — Synapses of the above fibres with the efferent neurones.
- Intermediate neurones omitted for simplicity. (Bayliss, 1908, Fig. 27.)

shows itself. He points out that the muscular coat of the arterioles may justly be regarded as the physiological antagonist of the cardiac muscle, so that an increase in the

strength of the contraction of the latter would be expected to be accompanied by an inhibition of the "tone" of the vascular musculature, as the contraction of a flexor is associated with inhibition of the corresponding extensor.

The reflex vaso-dilatation produced by stimulation of the depressor nerve is not confined to any particular region of the body. It appears to affect all parts supplied with vaso-motor nerves (Bayliss, 1893). There is thus no antagonism in general reflexes between the visceral and peripheral circulations. It may happen that an organ poorly supplied with such nerves may suffer a passive diminution owing to the fall of blood pressure, although its own vessels are actually relaxed. While the peripheral vaso-dilatation produced by depressor stimulation is universally distributed, there is evidence that the relative parts played by inhibition of constrictors and excitation of dilators differs according to the preponderance of either kind of nerve in the supply of a particular region. Thus, the viscera are apparently chiefly supplied with constrictors, while the vaso-dilators preponderate in the rest of the body. Ostroumov (1876, pp. 256 and 276) indeed ascribed the effect of the depressor to reflex stimulation of vaso-dilators on the ground of his experiments on the skin, laying stress on the fact that the temperature of a paw with normal nerve connections rises higher on stimulation of the depressor fibres than does that of the opposite paw when the nerves are cut, an operation which is, of course, equivalent to complete inhibition of constrictors.

Although there can be no doubt that the depressor endings are stimulated by rise of aortic pressure, it has been found difficult to prove the fact experimentally. When the blood pressure is high, it would be expected that the depressor nerves should be in action and that section of them would result in a rise of arterial pressure. This result

is not easy to obtain by experiment. I have seen it in the rabbit and Figure 41 is an illustration. Figure 42 shows that an impulse is sent through the depressor at each heart beat. The vaso-dilatation of a perfused organ, united by its vaso-motor nerves to the centres, found by Pilcher and



Figure 41.

Depressor tonus.

Rabbit. One depressor cut before the tracing. An intravenous injection of saline had also been given

At the break in the tracing, the second depressor was cut, giving rise to a higher level in the arterial pressure, presumably by removal of depressor impulses from the aortic receptors.

Upper signal is level of zero of arterial pressure.

Lower signal marks time in seconds.

Sollman (1914) to follow transfusion of blood, seems to show that the depressor nerve was stimulated thereby.

#### *FALL OF PRESSURE FROM OTHER NERVES.*

Although, as a rule, stimulation of the central end of an ordinary sensory nerve causes a reflex rise of blood

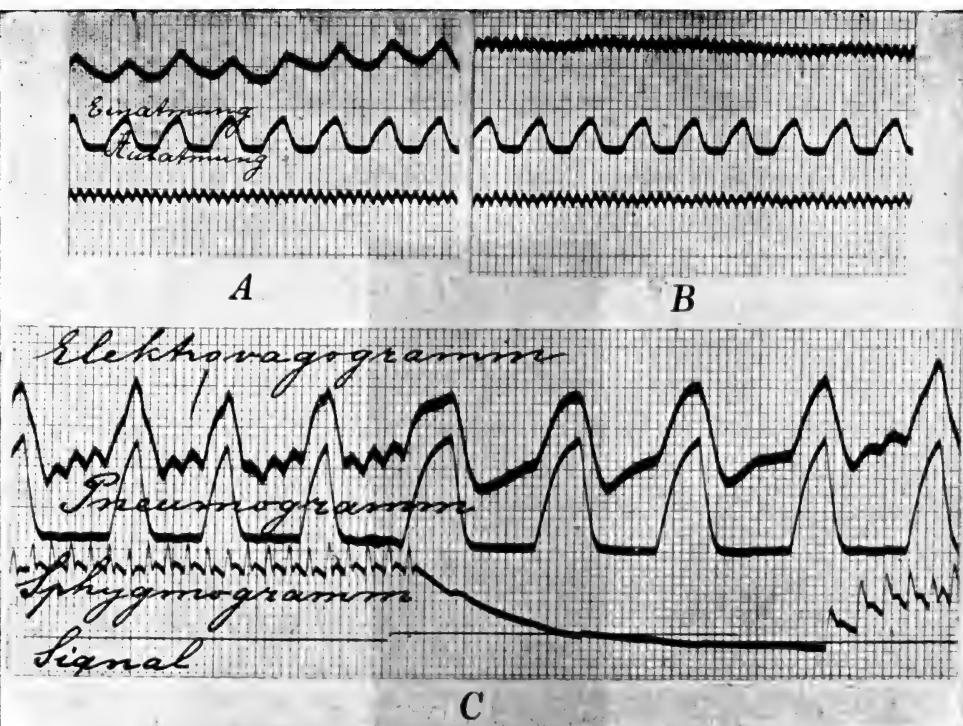


Figure 42.

Electrical Changes in the Vagus and Depressor Nerves. String Galvanometer.

*A. Vagus. Rabbit.*

1<sup>st</sup> curve from above — electrical change in that part of the cut vagus in connection with the lung. That is: afferent impulses from the lung.

2<sup>nd</sup> curve — respirations.

3<sup>rd</sup> curve — heart beats.

The only electrical change present is that due to pulmonary distension.

*B. Depressor. Rabbit.*

1<sup>st</sup> curve — electrical change in heart end of cut nerve.

2<sup>nd</sup> curve — respirations.

3<sup>rd</sup> curve — heart beats.

Electrical effects with heart beats only, none with respirations.

*C. Vagus (with depressor fibres). Dog.*

1<sup>st</sup> curve — electrical change in thoracic end of cut nerve.

2<sup>nd</sup> curve — respirations.

3<sup>rd</sup> curve — heart beats.

Both heart and lungs produce electrical changes. At the rise of the signal, the vagus of the opposite side was stimulated. Respiration continues, with its electrical effects, the heart stops and, together with it, the small waves in the depressor fibres.

(Einthoven.)

pressure by peripheral vaso-constriction, under certain conditions a fall of pressure may be obtained. This had been noticed by many investigators, but the first systematic account of the conditions necessary was given by Reid Hunt (1895). These conditions are either (a) stimulation of nerves cooled to about  $4^{\circ}$  C., or (b) stimulation at a certain stage of regeneration, or (c) weak stimulation, or (d) mechanical stimulation of afferent fibres in muscles. The conclusion is drawn that there are "depressor" fibres in the sciatic and other similar nerves. In view of the later work of Keith Lucas, we may conclude that their optimal rate of incidence of energy differs from that of the "pressor" fibres. Reid Hunt was unable to obtain differential effects by the use of varying rates of stimulation or the use of chemical stimuli. He also concludes that a reflex excitation of the vaso-dilator centre occurs in the fall of pressure from mixed sensory nerves.

Vincent and Cameron (1914) call attention to a source of fallacy in such experiments when made on uncurarized animals. The reflex acceleration of breathing by retarding the venous inflow into the heart brings about a fall in arterial pressure. But they also obtained reflex fall of blood pressure when this possibility was excluded. It is clear that the observation of a peripheral dilatation also excludes this fallacy.

Figure 43 illustrates the phenomenon of reflex fall of pressure.

Further facts bearing on the question will be found below under the headings of the course of the fibres in the spinal cord and the effect of drugs on vaso-motor reactions. It may be that the depressor fibres in ordinary nerves are afferent fibres from arteries, analogous to those of the depressor nerve, as suggested above. But the question requires investigation.

## PRESSOR REFLEXES.

With the exception of the depressor nerve, all afferent nerves contain fibres whose stimulation results in a reflex rise of arterial pressure. Such rise of pressure appears to be associated with the stimulation of nerve fibres whose expression would be that of pain in the un-anaesthetized animal. But loud noises are also said to produce a rise of blood pressure. In this latter case, the process is probably

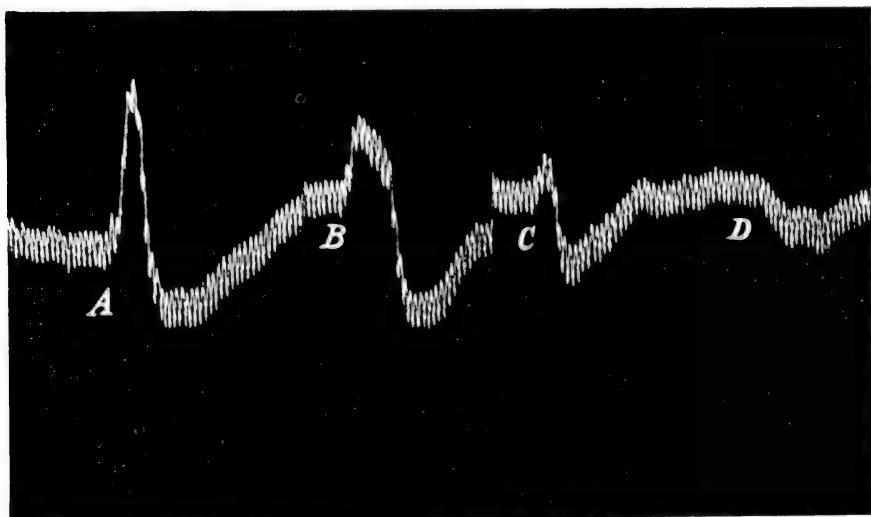


Figure 43.

Effects of Decreasing Strength of Stimulation on Vaso-motor Reflexes.

Dog. Central end of sciatic stimulated.

*A* Coil at 15 cm.

*B* Coil at 18 cm.

*C* " " 20 "

*D* " " 24 "

a more complex one, involving the participation of a greater number of neurones in the arc. The rise of pressure in general is, doubtless correctly, ascribed to an excitation of vaso-constrictor nerves by the intermediation of the vaso-constrictor centre.

But since we have seen that the opposite kind of reflex, the depressor, is composed of two reciprocal factors, it is necessary to see what evidence there is of both excitation of constrictors and of inhibition of tone in the dilator centre in the case of pressor reflexes.



Figure 44.

Excitation of Vaso-constrictors in Pressor Reflex.

Upper curve — vol. of hind limb of cat.

Lower curve — arterial pressure. Zero — 20 mm. below time signal.

The dilator supply was cut off by previous section of the spinal cord in the middle of the lumbar region; that is, on the cranial side of the outflow of these nerves.

Central end of median nerve stimulated at mark of upper signal. (Bayliss, 1908.)

Although the excitation of vaso-constrictors scarcely requires special proof, it is well for the sake of completeness to give a tracing in which any participation of vaso-dilators was excluded (Figure 44).

In order to detect the existence of the other component, inhibition of the vaso-dilator centre, it is obviously necessary that there should be a tonic state of excitation in this centre. This is not usually the case. A similar difficulty was met with by Sherrington in the investigation of reflexes to voluntary muscle, where the centres of the flexors are not in a state of excitation in decerebrate rigidity. For this reason, it is only under favourable conditions that it is possible to detect the occurrence of a vascular narrowing

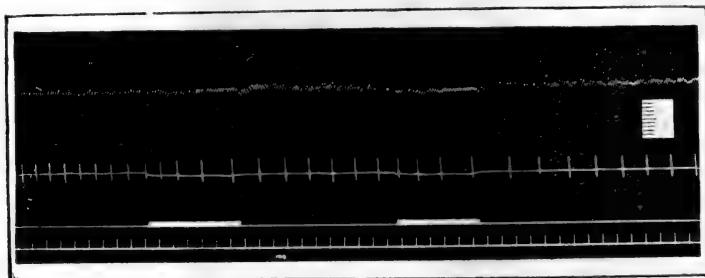


Figure 45.

Inhibition of the Vaso-dilator Centre in Pressor Reflex.

Upper tracing — Arterial pressure. Rabbit.

Top signal — drops of blood from submaxillary vein.

Vagi, sympathetics and depressor nerves cut on both sides, so that the gland was innervated only by the dilators of the chorda. Mercury compensator in use and evisceration performed, so that the normal rise of blood pressure from the two stimulations of central end of the vagus (pressor nerve in the rabbit) were prevented. The slowing of the rate of blood flow shows that the vessels were narrowed, although there was no constrictor supply.

after the constrictor supply has been cut. These conditions are, as might be expected, such as would probably be accompanied by tonic excitation of vaso-dilators, such as high blood pressure, plethora, high temperature, and so on. Figures 45 and 46 are given as cases which can only be satisfactorily explained as due to inhibition of the vaso-dilator centre.

## BALANCE EFFECTS.

It will be remembered that Sherrington, in the case of reflexes to voluntary muscle, showed that if excitatory and inhibitory nerves are stimulated at the same time, the effect is an algebraic sum, such that, at appropriate relative strengths, one effect exactly neutralizes the other and the result is zero.

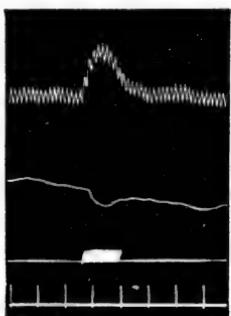


Figure 46.

## Inhibition of Vaso-dilator Tone in Pressor Reflex.

Upper curve — arterial pressure. Zero — 30 mm. below time signal.

Lower curve — volume of external ear of rabbit.

Vaso-constrictor supply cut off by section of cervical sympathetic.

The signal marks a stimulation of the central end of the median nerve. The rise of pressure is accompanied by constriction in the ear, although the only vaso-motor nerves intact were dilators. (Bayliss, 1908.)

I obtained similar results with vaso-motor reflexes in 1893, previous to Sherrington's work on voluntary muscles, but did not make a regular series of experiments. In Figure 47 the strength of stimulation of the excitatory nerve was just sufficient to balance for a time the simultaneous stimulation of the depressor. A figure showing intercurrent stimulation of the depressor balancing that of the anterior crural will be found in the original paper. Figure 48 shows that a similar antagonism exists between the depressor and asphyxial stimulation of the centre.

Martin and Stiles (1916) made a more systematic study of the results obtained when the relative strength of the

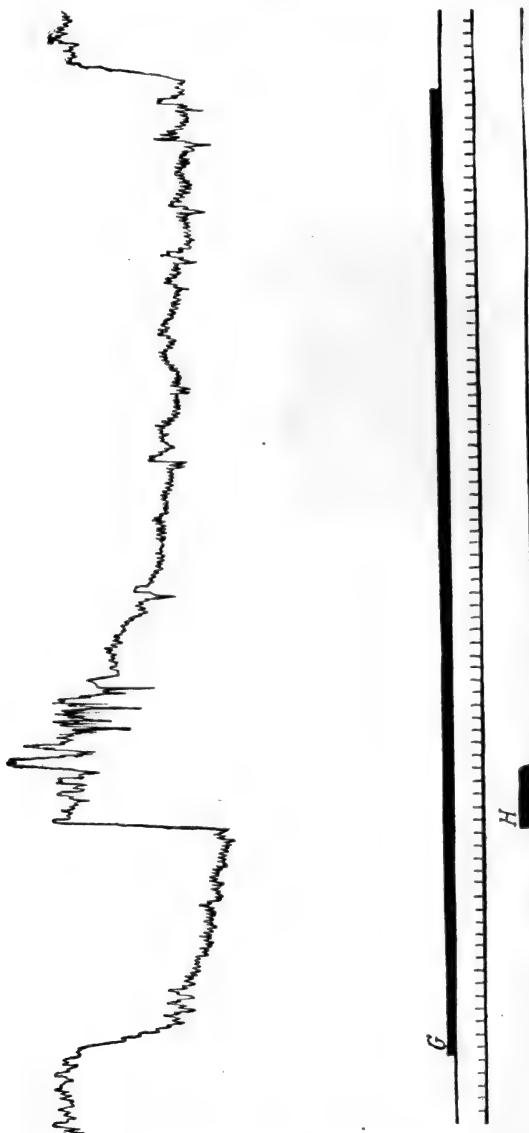


Figure 47.

Balance In Vaso-Motor Reflex.

Arterial pressure of rabbit.

Signal *G* marks duration of stimulation of depressor nerve.

Signal *H*, that of central end of anterior crural nerve.

Normal level before *G*. Depressor stimulation causes it to fall, but concurrent stimulation of a pressor nerve brings it back to normal. The fall returns when the pressor effect disappears, but returns to normal when the depressor effect ceases. (Bayliss, 1893, Fig. 21.)

opposing stimuli was varied. Figure 49 reproduces some of their curves. They found that strong depressor stimuli

can be antagonized by strong pressor stimuli. The figure shows that weak stimulation of either nerve can be over-powered by strong stimulation of the opposite one, so that the effect of the weaker one may appear to be absent.

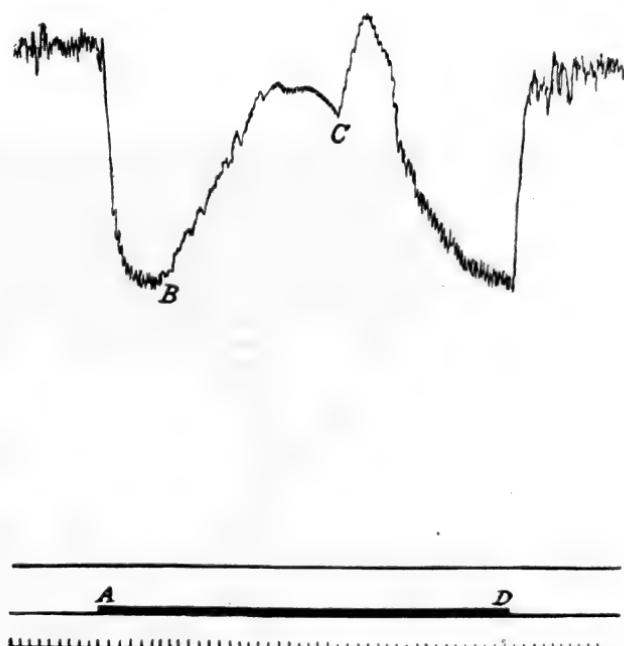


Figure 48.

Antagonism of Depressor Inhibition and Asphyxial Stimulation of the Vasoconstrictor Centre.

Rabbit, curarized. Arterial pressure.

Depressor stimulated from *A* to *D*.

Stopping the artificial respiration at *B* brought back temporarily the pressure to nearly normal. Respiration was resumed at *C* and, as the asphyxial state disappeared, the depressor fall came on again until the stimulation of the nerve ceased.

(Bayliss, Jl. Physiol. 1893, Fig. 24.)

If depressor stimulation is strong, however, it is very difficult to do more than neutralize it, whatever the strength of the pressor stimulation.

## LOVÉN REFLEXES.

In many cases in which the central end of an afferent nerve from an organ could be stimulated without interruption of the vaso-motor fibres, which were carried by another nerve, it was found that the pressor response of the general arterial pressure was not contributed to by a

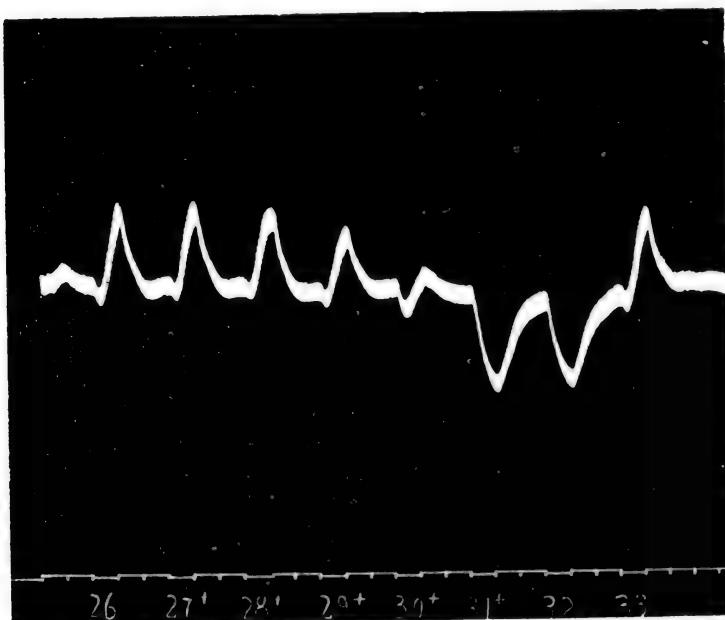


Figure 49.

## Vaso-motor Opposition.

In the first stimulation marked on the signal, the central end of the peroneal nerve alone was stimulated. In the next five (27 to 31), the same constant strength of stimulus of this (pressor) nerve was opposed by a depressor stimulation of increasing intensity, as indicated by the numbers in Martin Z. units. The 7<sup>th</sup> (No. 32) is the effect of the depressor alone; the 8<sup>th</sup> (Nr. 33), that of the peroneal alone.

(Martin and Stiles, 1916, Fig. 2. Amer. Jl. Physiol.)

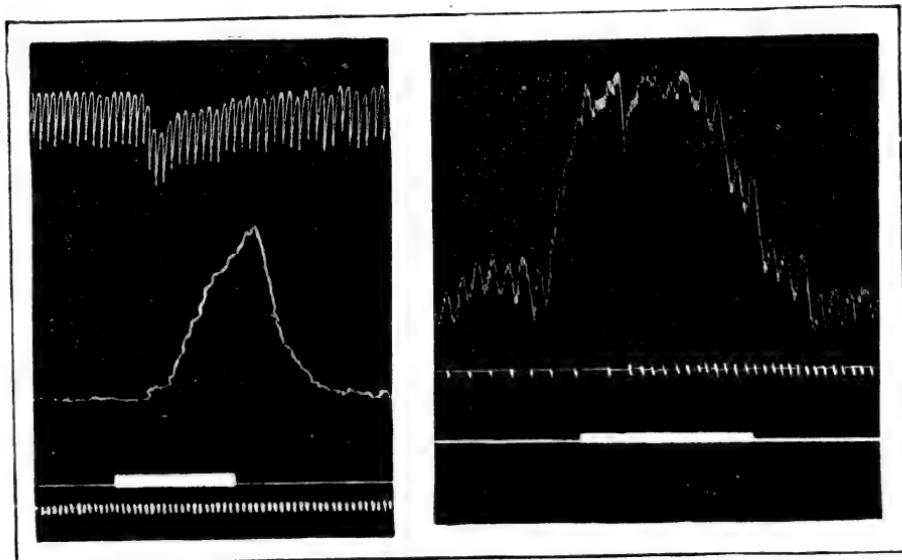
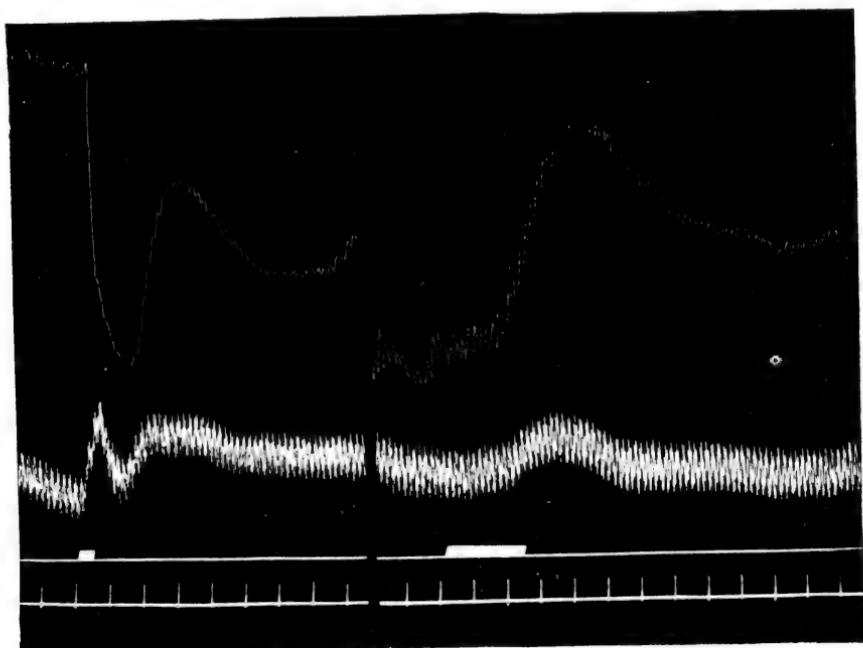
*A**B**C**D*

Figure 50.

Lovén Reflexes.

[Explanation next page.]

vaso-constriction in the organ in question, but that an actual vaso-dilatation occurred therein. Lovén (1866) first described the phenomenon in the rabbit's ear on stimulation of the posterior auricular nerve, and in the case of the saphenous artery when the dorsalis pedis nerve was stimulated. Bradford (1889) found that stimulation of the central ends of the dorsal roots of the kidney area caused vaso-dilatation in the kidney. It is probable that the effect would be found to be more or less common to all organs if the appropriate nervous channels could be stimulated apart from the vaso-motor nerves. Figure 50 gives examples.

In some cases, the reflex dilatation spreads to the corresponding organ of the opposite side, but this is not very common.

I found that reciprocal innervation holds here as in the general depressor reflex; that is, the dilatation is due both to excitation of dilators and to inhibition of constrictor.

[Explanation to Fig. 50.]

*A* Upper curve — blood pressure.

Lower curve — volume of upper part of hind leg of dog.

At the signal, the central end of the dorsalis pedis nerve of same leg was stimulated, causing a marked dilatation of the leg, with a slight fall in blood pressure. The usual rise of general pressure was absent here.

*B* Upper curve — blood pressure.

Lower curve — drops of blood falling from cut femoral vein.

At the signal, the central end of the anterior crural nerve of the same side was stimulated. A rise of blood pressure is seen, accompanied by vaso dilatation in the leg. Fig. 44 above shows that stimulation of a sensory nerve from another region, namely, that of the arm, causes vaso-constriction in the leg. The fact is also seen in

*C* Upper curve — volume of hind leg of dog.

Lower curve — blood pressure.

Vaso-dilators cut off by section of lumbar and sacral dorsal roots.

At the signal, the median nerve was stimulated. Rise of pressure, with constriction of the leg.

*D* Same experiment as C, but the central end of a dorsal root of the leg area, the sixth lumbar, was stimulated.

There is also rise of blood pressure, but the vessels of the leg dilate.

tone. The last tracing of Figure 50 shows that the latter occurs and Figure 51 that the former is involved. The rapidity of the dilatation may invite some suspicion in Figure 51, but the animal was fully curarized and the greatest care was taken that no muscular contraction occurred. There was also a distinct latent period, not ob-

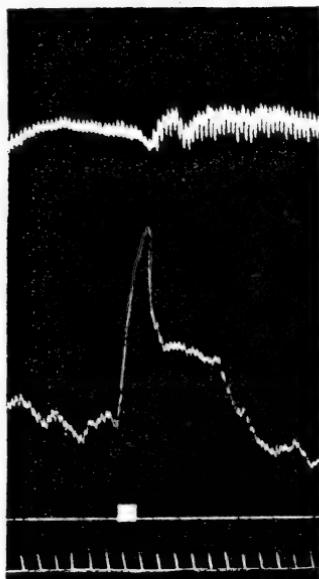


Figure 51.

Excitation of Vaso-dilators in Lovén Reflex.

Upper curve — blood pressure.

Lower curve — volume of hind limb of dog.

Abdominal sympathetics extirpated, viscera removed.

At mark of signal, central end of anterior crural nerve of same leg stimulated.

(Bayliss, *Jl. Physiol.* 1902, Fig. 9.)

vious on the tracing owing to the slow rate of movement of the paper, a fact which also exaggerates the suddenness of the rise of the lever.

The local nature of these reactions suggests that they are of spinal origin. In such a case, the nerve connections

may be represented somewhat as in Figure 52. But this question awaits further investigation.

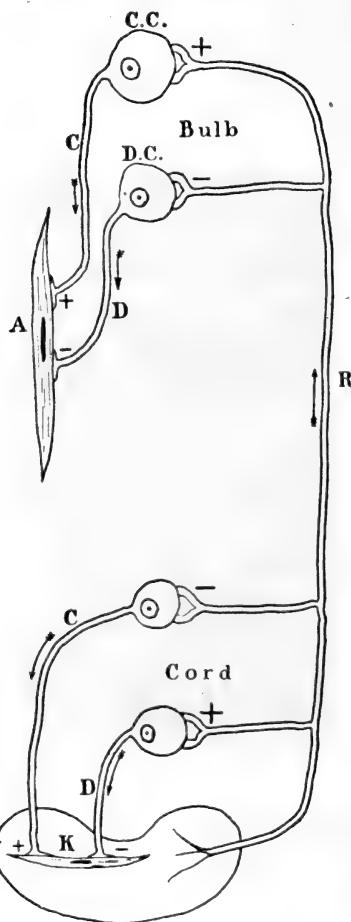


Figure 52.

Diagram of Lovén Reflex.

*C* and *D* — Constrictor and Dilator efferent neurones.

*A* Arterial muscle-cell of body generally.

*K* " " of organ (e. g. kidney) from which the afferent fibre, *R*, passes to bulbar centres, giving off collaterals to the spinal centres. The connections of this fibre are such that it excites constrictor centres in the bulb and dilator centres in the spinal cord, while its relations to the dilator centre in the bulb and the constrictor centres in the cord are inhibitory.

(Bayliss, 1908, 1.)

The fact that the arterioles of certain organs appear to be dilated by specific substances, which have no marked action on those of other organs, may possibly be due to the existence, in the walls of the former vessels of receptors sensitive to such substances. The response of the renal vessels to urea and to glucose may be mentioned. If this is the case, the reaction would be in the nature of a Lovén reflex and might be tested by section of the nerves.

#### *THE SITUATION IN THE SPINAL CORD OF THE PRESSOR AND DEPRESSOR FIBRES.*

According to Ranson and Billingsley (1916), the fibres which conduct the pressor impulses run in Lissauer's tract and are identical with the protopathic pain fibres of Head. This agrees with the observation made by Head and myself that the first vaso-motor reaction to be obtained from the central end of the regenerating radial nerve is a rise of blood pressure and that this occurs at a stage in which only protopathic fibres are present, namely, four weeks after nerve suture. The contrary results obtained by Reid Hunt (1895) were probably due to the nerves in his cases having reached a further stage of regeneration, the date being five to six weeks.

The rise of blood pressure may thus be regarded as a part of what may be called the "nociceptive syndrome", which consists of a general protective reaction against injury. It includes reflexes to voluntary muscles, secretion of adrenaline and so on. As appropriate to the mode of production, the reaction requires a somewhat powerful stimulus to set it going.

The *depressor* fibres are stated by Ranson and Billingsley to pass in a region of the lateral columns identical in situation with the spino-thalamic tract. But they are clearly

not the same fibres because the depressor reflexes are still present after the brain in front of the corpora quadrigemina has been removed, as in the "decerebrate preparation" of Sherrington. I have already made the suggestion that they may be afferent fibres from the blood vessels themselves. It seems likely that arteries other than the arch of the aorta should be supplied with "depressor" fibres. An additional protection would be given against a dangerously high blood pressure. What experimental evidence there is has been referred to above (p. 42), but the problem needs further research.

#### *THE ACTION OF DRUGS ON VASO-MOTOR REFLEXES.*

*Strychnine.* Sherrington has shown that the inhibitory component of reflexes to voluntary muscles is converted into an excitation by this drug. Thus, a reflex causing flexion of the knee-joint, which is produced by contraction of flexors together with inhibition of extensors, is, after strychnine, converted to simultaneous contraction of both antagonists. Since the action of the depressor nerve is, at all events in great part, an inhibition of the constrictor centre, Sherrington tested the action of strychnine on this reflex. He found that, under certain conditions, the fall of blood pressure was converted into a rise. The further investigation of the question was undertaken by myself (1908). It turned out that, if sufficient strychnine be given, the phenomenon can regularly be observed (Figure 53). Rabbits are, doubtless, comparatively insensitive to strychnine, but it is remarkable that the dose required is sufficient to paralyze the vaso-constrictor reflexes from sensory nerves, and may amount to as much as 7 centigrams. This fact in itself excludes the possibility of the result being due to escape of current to sensory nerves in the neighbourhood

and the stimulation of problematical sensory fibres in the depressor itself. The electrodes may be placed on various other structures in the neck without any effect, since the pressor reflexes from these are already paralyzed. Langley (1912), however, was unable to obtain this reversal. I am inclined to think that the dose he gave was insufficient, because he found recovery to occur. In my experiments, no recovery occurred as long as the experiment lasted.

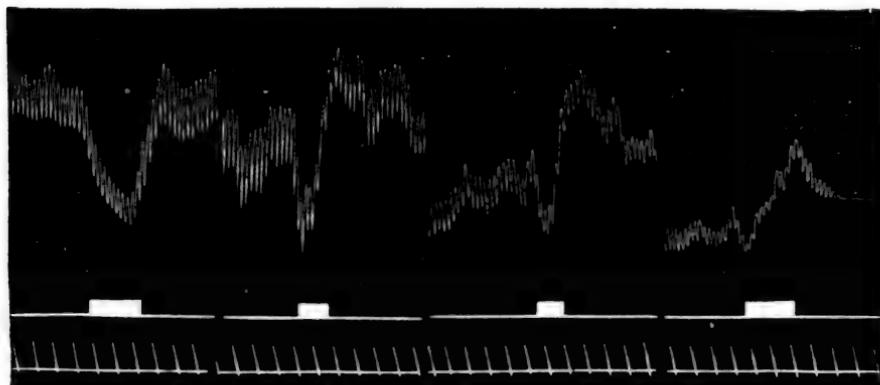


Figure 53.

Reversal of Depressor by Strychnine.

Rabbit. Blood pressure curve.

First stimulation — normal state.

Second stimulation — after one dose of strychnine.

A further dose given between each stimulation.

(Bayliss, Proc. R. S., 1908, Fig. 15.)

Possibly the fact that Langley used rabbits decerebrated by injection of starch suspension, which is apt to be uncertain in the distribution of the vessels blocked, may have had some part to play in his results. Although the effect can be obtained in the cat and dog, and with smaller doses than in the rabbit, the interpretation is more difficult, because the depressor fibres are generally conveyed in the trunk of the vagus along with pressor fibres from various

sources, so that the possibility cannot be definitely excluded that the former might be paralyzed before the latter. Evidence will be given presently, however, that such an explanation is very improbable. Even when the depressor is a separate nerve in the cat, it remains a mixed nerve. Langley reports an experiment on a decerebrate rabbit in which stimulation of the depressor caused regularly a slight muscular movement and thinks it probable that the depressor in this animal contains a certain admixture of pressor fibres. But fall of blood pressure from any cause is liable to bring about some movement in very excitable animals.

This rise of blood pressure obtained from the depressor under strychnine is shown by plethysmographic tracings to be due to a peripheral vaso-constriction, just as a typical pressor reflex is.

Further investigation of the action of strychnine led to interesting results with regard to the mechanism of vaso-motor reflexes. Their description will be facilitated by aid of Figure 54.

In the previous diagram (Figure 40), for the sake of simplicity, no intermediate neurones were inserted. In Figure 54, a special intermediate neurone on the excitatory side of both the pressor and depressor reflexes is indicated, because a complete explanation of the phenomena connected with the action of strychnine and chloroform requires its presence. Of course, there may be, and probably are, additional neurones present in all the arcs. Those shown are intended to represent the existence of certain elements on the excitatory side which are absent on the inhibitory side, and are the minimum possible.

We may proceed, in the first place, to analyze the behaviour of the vaso-constrictor centre, as we commenced with this. We saw that the inhibition of this centre by the *depressor* nerve is converted by strychnine into an ex-

citation. In the diagram, the minus sign at *a* becomes a plus sign. This is shown by the rise of blood pressure and the peripheral vaso-constriction. The effect of this drug on the excitatory component of the reflexes is otherwise; a small dose usually increases it, but further doses

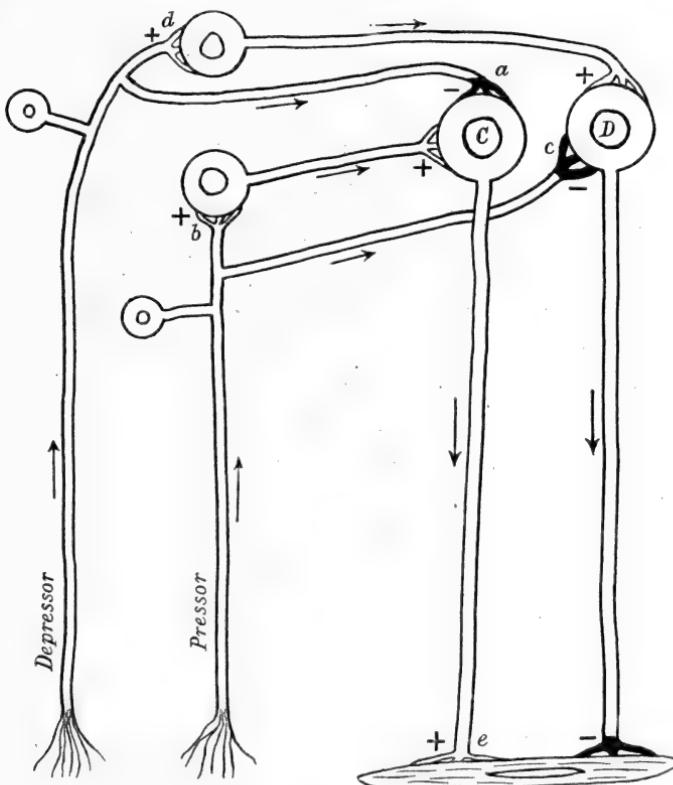


Figure 54.

Diagram of the Action of Drugs on Vaso-motor Reflexes.

*C* — Constrictor centre.

*D* — Dilator centre.

Inhibitory synapses black and marked —.

Excitatory synapses left white and marked +.

Synapses *a* and *c* are reversed by strychnine, not affected by chloroform.

*b* and probably *d* are reversed by chloroform.

*b* and *d* are paralysed by Strychnine.

*c* is possibly reversed by ergotoxine.

paralyze it. Thus, that dose of strychnine which converts *a* into + abolishes the action of a pressor nerve through *b*. That this latter effect is not on the centre itself but somewhere on the afferent side is shown by the persistence of the reversed vaso-constriction from the depressor at a dose which paralyzed the constrictor reflex from pressor nerves. Whether the neurone itself is affected or the synapse at *b* is not decided by the experiment, but from Sherrington's work, the latter is the more probable.

Passing to the behaviour of the vaso-dilator centre, it would naturally be expected to be similar to that of the vaso-constrictor centre, although the effects on the blood pressure would be opposite. At the beginning of my work on the question, the existence of this centre was left out of consideration and various puzzling phenomena were noticed. Thus, in order to observe the state of the blood vessels in separate organs without the confusing passive effects due to changes in the general blood pressure, the abdominal viscera were removed. After such a procedure, it was usually found impossible to obtain reversal of the depressor fall by strychnine, whereas a comparatively small dose of the drug reversed the rise of pressure previously obtained from a sensory nerve into a fall. In other experiments, the abdominal and cervical sympathetics were cut, in addition to evisceration, thus leaving only a comparatively small part of the body supplied with constrictors, while the greater part was left with its dilator supply intact. In such preparations, the effects mentioned were always obtained (see Figure 55). It will be seen that, owing to the preponderance of constrictors in the viscera and of dilators in the skin, we had removed nearly all of the former, while leaving most of the latter. Thus, experiments were made on an animal in which the vaso-constrictor centre was unable to produce anything but small peripheral

effects, while the dilator centre was still able to control the greater part of its territory. Strychnine may thus under certain conditions reverse a reflex fall of pressure into a rise; under other conditions, a reflex rise into a fall. Further tracings will be found in my paper (1908, 1, p. 362).

The obvious explanation of the absence of vaso-constriction from the depressor nerve and the persistence of the vaso-dilator effects in an animal under strychnine after

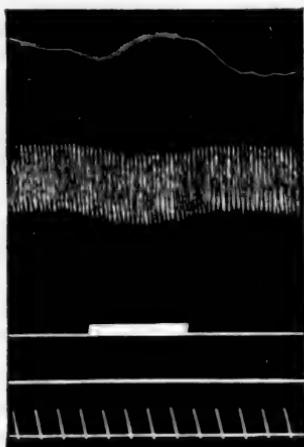


Figure 55.

Reversal by Strychnine of Inhibition of Dilator Centre in Pressor Reflex.

Rabbit. Eviscerated. Cervical and abdominal sympathetics cut. Strychnine. Upper curve — volume of ear.

Lower curve — arterial pressure.

Stimulation of the median nerve causes fall of blood pressure and dilatation of the ear by means of excitation of dilator nerves in place of the normal inhibition of dilators of a pressor reflex. (Bayliss, Proc. R. S., 1908, 1, Fig. 20.)

evisceration and section of the sympathetics, as in the experiments referred to, is that the former is due to reversal of the inhibition of the vaso-constrictor centre, so that in the almost complete absence of organs with such a supply, the result could not be manifested. The excitatory component of the reflex, the excitation of vaso-dilator nerves,

remains able to show itself, possibly somewhat increased by the drug. The fall of pressure from the depressor here is due to reflex excitation of the dilator centre and excitation is not reversed by strychnine. In the diagram of Figure 54, the effect through *d* is that which shows itself in the eviscerated, "dilator", animal, whereas in the normal animal it has but a subordinate place.

The explanation of the fall of pressure from pressor nerves after strychnine is clearly due to conversion of the normal inhibitory effect of these nerves on the vaso-dilator centre to an excitation. In the figure, the sign of the effect at *c* is reversed. The effect through *b* is very small, because of the relative absence of vaso-constrictors and is easily overpowered.

The action of strychnine on the blood pressure, apart from the stimulation of nerves, is a rise, due to stimulation of both centres, the vaso-constrictor one being the more powerful. The effect is, no doubt, brought about by the drug making the centres more excitable, so that a larger effect is produced by the peripheral stimulation always present to some extent. That the vaso-dilator centre is actually stimulated is shown by the fact that, instead of a rise, a fall of blood pressure is produced by a dose of the drug in the eviscerated, "dilator", preparation. If the first dose of strychnine has been fairly large, it is found that a second dose causes a fall of pressure, even in the intact animal. This appears to be due to early paralysis of the intermediate neurone, *b*, combined with commencing reversal of the effect at *c*. That it is really an excitation of dilators is shown by the fact that organs deprived of their constrictor supply dilate. Such an explanation is confirmed by the action of cocaine, which normally causes a rise of blood pressure by excitation of constrictors, but when preceded by strychnine, a fall of blood pressure results

from an injection. Adrenaline, which acts peripherally, on the other hand, produces its normal rise after strychnine. The excitatory phase of the pressor reflex, as already mentioned, is paralyzed by a smaller dose of strychnine than the excitation of dilators in the depressor reflex, but in both cases a smaller dose is required than that to paralyze the reversed inhibitory phases of the two reflexes. Perhaps this is due to the special sensibility of the intermediate synapses and may be connected with the fact that strychnine reverses, before it paralyzes, the inhibitory phases.

On account of the peculiar nature of the reversed depressor vaso-constriction in being so much more resistant to strychnine than the vaso-constriction from pressor nerves is, it should be made clear that the absence of a vaso-constriction from the median nerve after a dose of the drug in the normal animal is not due to a balance from the simultaneously excited vaso-dilator centre. If the spinal cord in the cat be divided at the second lumbar segment, the vaso-dilators of the hind leg are cut off from the centre. Under such circumstances, if the vaso-constrictors are really being excited, but masked, their effect would be shown in the leg. On the contrary, no effect was seen after strychnine, although it was present before the action of the drug.

In the interpretation of the effects of strychnine given above, the hypothesis originally put forward by Sherrington, namely, that the inhibitory process is converted into an excitatory one, has been adopted. Another possible explanation of the action of the drug might be given. The depressor, for example, might be connected, through intermediate neurones of an excitatory nature, with the vaso-constrictor centre, but through synapses normally impermeable to impulses. Under strychnine, they might become

permeable at a time when the inhibitory impulses were weakened or abolished. The long latent period of the reversed effect is evidence against this view. It is usually 18 to 25 seconds, whereas the normal effect from the median nerve has at most a latent period of two seconds. The synapse might certainly be only partially permeable. The question, however, cannot be regarded as decided yet (see Sherrington and Owen, 1911, and Cushny, 1919).

The inhibitory component of the Lovén reflex is also reversed by strychnine.

Other drugs which increase the excitability of the bulbar centres have the same action as strychnine; cocaine has been referred to; thujon, the active principle of absinthe, and chloralose may be added. Sherrington has shown that tetanus-toxin reverses inhibition to excitation in the case of the skeletal muscles.

*Chloroform.* This substance is recognized as a pharmacological antagonist to strychnine, so that its action might be expected to be of an opposite nature. If strychnine converts an inhibitory effect into an excitatory one, chloroform should convert an excitatory reflex into an inhibitory one. I found this to be the case in vascular reflexes (1908, 1), while Sherrington and Sowton (1911) extended the evidence to the reflexes to voluntary muscles. The complete investigation of all aspects of its action on vaso-motor reflexes is very difficult, since a large dose is required and there is a very narrow margin between the reversal effect and complete paralysis. Moreover, chloroform has a general depressant action on all functions. Cyon in 1870 showed that the fall of blood pressure often observed on stimulation of sensory nerves in the rabbit, and supposed to be the rule in this animal, was due to the fact that chloral, which has the same action as chloroform, was used. He attributed the phenomenon, erroneously, to effects on the cerebral

cortex. A far larger dose is required than that for complete paralysis of the cortex.

Figure 56 shows the general effect. Stimulation of the central end of the median nerve under ether gave the typical rise of blood pressure with constriction of the kidney. Chloroform was then given until the blood pressure fell to

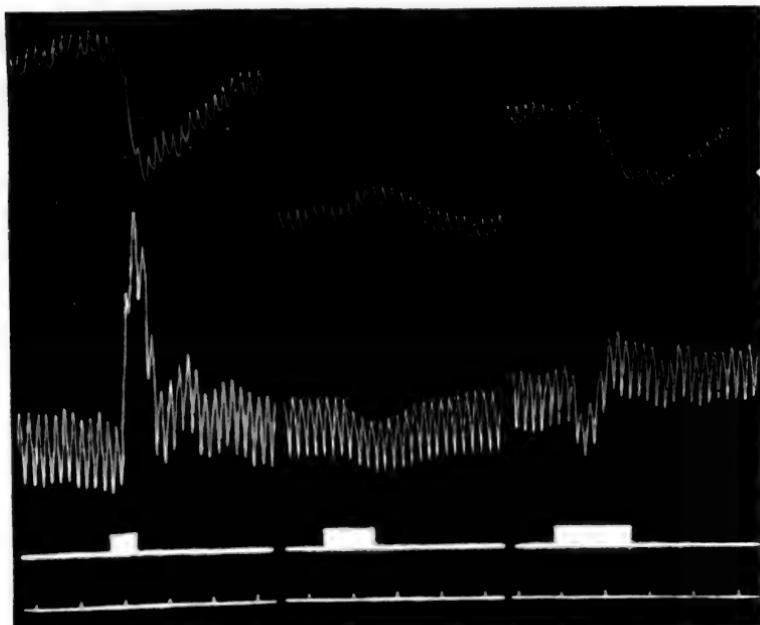


Figure 56.

Effect of Chloroform on Pressor Reflexes.

Rabbit.

Upper tracing — volume of the kidney.

Lower tracing — arterial pressure. Zero = 23 mm. below upper signal.

Median nerve stimulated.

First stimulation under ether alone.

Second do. — under chloroform.

Third do. — after partial recovery from chloroform under ether.

(Bayliss, 1908, 1, Fig. 24.)

6.4 mm of mercury. Repeating the stimulation, a fall of pressure was obtained, along with dilatation of the kidney. Return to ether restored the original state of affairs.

Analysis was necessary and was made in a way analogous to that of the strychnine effect. In the first place, it was found that no reversal effect could be obtained in the eviscerated animal, although chloroform was given up to a lethal dose. The result can only be explained as a manifestation of the normal inhibition of the dilator centre, which was unmasked owing to the absence of the opposing

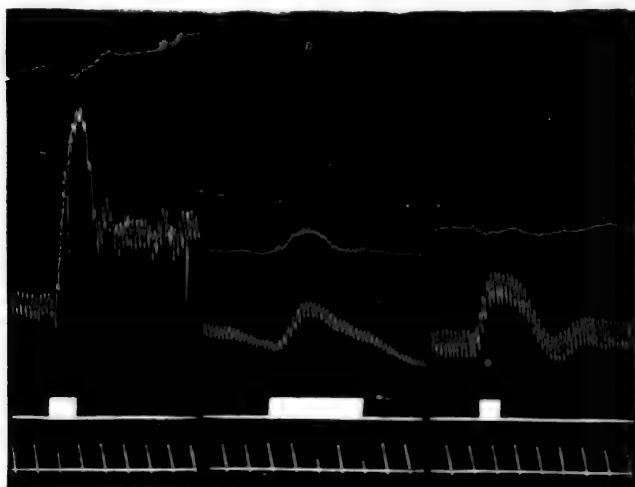


Figure 57.

Reversal by Chloroform of Excitation to Inhibition of Constrictors.

Upper tracing — volume of hind limb. Vaso-dilators cut.

Lower do. — arterial pressure. Zero — lower in 2<sup>nd</sup> and 3<sup>rd</sup> than in 1<sup>st</sup> tracing.  
Stimulation of central end of median nerve.

1<sup>st</sup> under ether.

2<sup>nd</sup> under chloroform.

3<sup>rd</sup> after partial recovery under ether again.

(Bayliss, 1908, 1, p. 367.)

inhibition of constrictors. This absence was due to removal of the large visceral area of constrictors. Figure 57 gives further evidence. The rabbit was eviscerated and the spinal cord cut at the second lumbar segment, so that the hind leg, in a plethysmograph, could only show effects due to

vaso-constrictors. The first part of the figure gives the effect of stimulating the median nerve under ether. We see the normal rise of pressure and the constriction of the limb. Chloroform was then given until the blood pressure fell by 70 mm. As mentioned above, stimulation of the pressor nerve still gave a rise of pressure, but it was accompanied by dilatation of the limb, shown both by increase in volume as well as of pulsation. This result can only mean that the previous excitation of constrictors was converted into an inhibition of the centre, since this was the only way in which dilatation of the limb could be produced. Thus, in the eviscerated animal, inhibition of the constrictor centre is still present, but its general effect is overpowered by the simultaneous inhibition of the dilator centre. The third curve represents a stage of partial recovery under ether again.

No evidence of any effect on inhibitory processes other than ultimate paralysis was obtained.

The conversion of a depressor fall in an eviscerated animal into a rise by inhibition of the dilator centre was only partially seen. The difficulty of obtaining tone in the dilator centre was doubtless responsible for the failure.

There is evidence that the fall of arterial pressure brought about by the administration of chloroform is partly due to peripheral dilatation. Such a dilatation may sometimes be seen in plethysmographic tracings of intestine or limb when the blood pressure is not falling too rapidly to mask it. Afferent pressor stimuli are being continually received by the constrictor centre. Under chloroform, these stimuli would cause inhibition of constrictor tone. Occasionally, again, an eviscerated, "dilator", animal may show a rise in arterial pressure by the action of chloroform. This may be explained by an inhibition of dilator tone, as in the case of a pressor stimulus under the same conditions.

## DIRECT INFLUENCE ON CENTRES.

The rise of pressure produced by strychnine is, of course, indirectly due to its increasing the excitability of the vaso-constrictor centre, so that, in the absence of peripheral stimuli, it would probably be absent.

On the other hand, *asphyxial blood* has a direct effect in exciting the bulbar centres. In asphyxia, as ordinarily produced experimentally by cessation of pulmonary ventilation, there are two changes in the blood proceeding

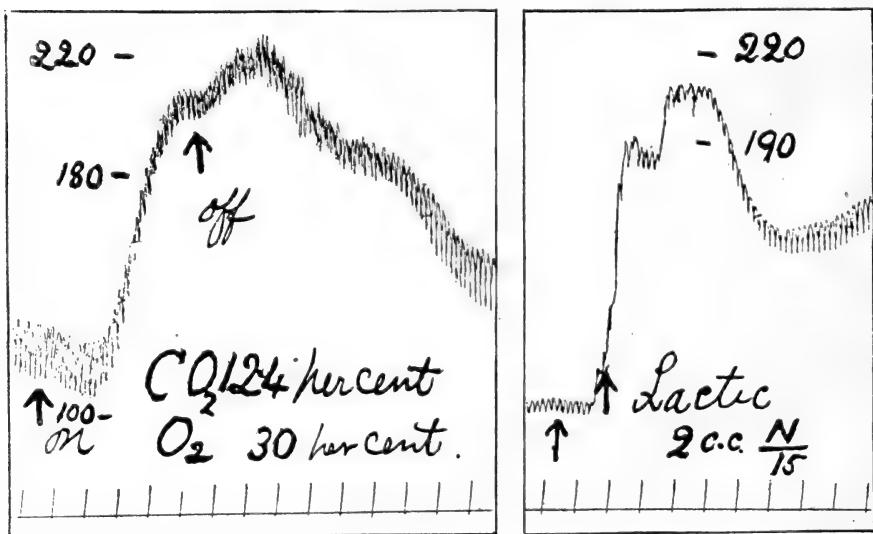


Figure 58.

Effect of Acids on Vaso-constrictor Centre.

Curarized, decerebrate, cat. Arterial pressure.

(Mathison.)

together, either or both of which might excite the vaso-motor centres. These are — accumulation of carbon dioxide from oxidation in the tissues, and deficiency in the supply of oxygen, as this gas rapidly becomes used up. Traube (1864, 1865) showed that carbon dioxide was capable

of causing a rise of blood pressure, by stimulation of the vaso-constrictor centre, in the absence of any lack of oxygen. In his experiments, rabbits were caused to breathe a mixture of 21 per cent, carbon dioxide with excess of oxygen. On the other hand, Marés (1902) obtained a similar effect with deficient oxygen, although carbon dioxide was not allowed

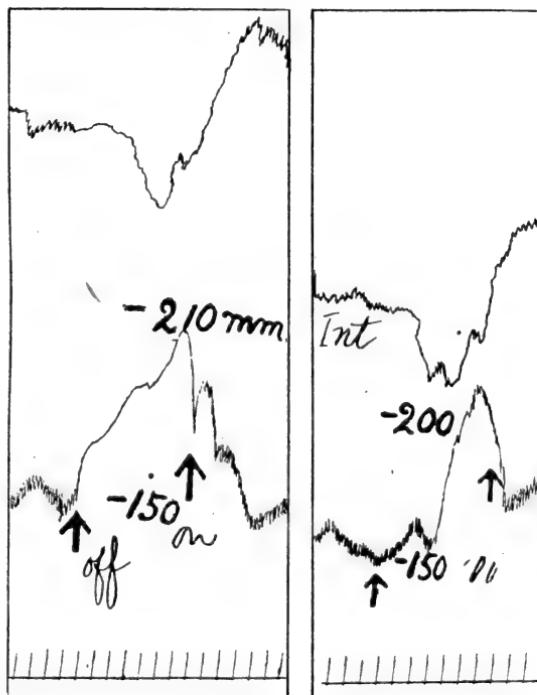


Figure 59.

Effects of Asphyxia and of Want of Oxygen.

Cat, decerebrate, curarized.

In the first tracing, artificial respiration stopped between the arrows.

In the second, Nitrogen substituted for air between the arrows. (Mathison.)

to accumulate. This was done by allowing animals to breathe mixtures of air and nitrogen in various proportions. The question was subjected to a renewed investigation by Mathison (1910, 1911), who showed clearly that the

constrictor centre is excited in both cases (Figures 58 and 59).

The chief difference is that, in a curarized animal, the rise of blood pressure commences practically at once when artificial respiration is stopped, whereas half a minute or more may elapse before the effect of breathing nitrogen is seen and then the onset is rapid. In figure 58, we see that the injection of acid has a similar effect to that of carbon dioxide and at first one might regard this as a proof that an increase in hydrogenion concentration is the active agent. Although this is probably the case, since it has been shown to be so with the respiratory centre, it must be remembered that the amount of acid injected is not sufficient to neutralize the whole of the bicarbonate in the blood, so that the action on the centre is really that of carbon dioxide when acid is injected into a vein. In some of Mathison's experiments, however, acid was injected into the central end of one of the carotid arteries and in this case it is probable that free acid reached the bulb before it had become completely neutralized; but the proof is not altogether complete.

The spinal centres are much less excitable both to carbon dioxide and to deficient oxygen (Kaya and Starling, 1909; Mathison, 1910), but the phenomena are otherwise similar to those of the bulbar centres.

On account of the similarity between the action of deficient oxygen and of injection of acids, Mathison came to the conclusion that when the nerve-cells are deprived of oxygen, after a certain time acid substances are produced within them. This production is not a normal steady process, like the formation of carbon dioxide, but comes on suddenly at a stage when the cell-mechanisms are beginning to be disorganized. Thus the process is pathological, while the stimulation by carbon dioxide is the normal one, as Frédéricq (1897) maintained.

It should not be left unnoticed that the production of lactic acid in the organism under defective oxygen supply, as investigated by Araki and his coadjutors (1891), might have its origin in the muscles only. This acid plays so important a part in the normal processes of muscular activity, that special investigation is required to show that it arises in tissues of other kinds. It is difficult to find satisfactory proof that nerve cells become acid when deprived of oxygen. Some old observations by Du Bois Reymond and others on the acidity of nerve centres after death were disputed by other workers. Renewed investigation seems desirable. On the other hand, if glucose is burned for energy purposes by cells in general, as is no doubt the case, and if it passes through the stage of lactic acid in the process, for which there is much evidence, it seems most likely that the first stage of glucose metabolism, which involves no consumption of oxygen, may be carried on in asphyxiated cells, but proceed no farther, unless oxygen is supplied.

Under certain circumstances, the fact can be ascertained that both the vaso-constrictor and the vaso-dilator centres are stimulated in asphyxia, but the effect of the former usually preponderates. When, however, the pressor effect from sensory nerves has been paralyzed by strychnine, asphyxia may show a stimulation of the dilator centre by the production of a peripheral dilatation of an organ in a plethysmograph (Bayliss, 1908 1, p. 356).

There is no rise of blood pressure in asphyxia in animals under a rather large dose of strychnine, although the actual efferent neurone is not paralyzed, as shown above. The fact shows that the action of asphyxial blood is exercised on some intermediate neurone on the excitor branch of the pressor reflex, presumably that one paralyzed by strychnine.

Asphyxia causes rise of blood pressure in a rabbit under a dose of chloroform sufficient to reverse the action of a pressor nerve. This fact serves to confirm the view taken above that the action of chloroform is not on the cell-body of the efferent neurone, so far as the conversion of excitation into inhibition is concerned.

*Traube Curves.* These are rhythmical waves in the arterial pressure, caused by periodic discharges from the centre (see Fig. 29, p. 59 above). They may be excited either by carbon dioxide or by want of oxygen (Mathison), and may appear in the action of certain drugs, such as absinthe, on the centres. They were first described by Traube (1865) and by Hering (1869). Apparently, the rise of blood pressure flushes out the centre by a greater blood supply and removes temporarily the cause of the stimulation, so that the pressure falls and the original state of the centre returns, and so on.

The waves known by the name of Mayer have been shown to be produced by the artificial respiration and to have merely a mechanical origin.

*Potassium.* It has been already mentioned that the action of acids on peripheral arterioles is to relax them, so that its effect on the nerve centres is of an opposite nature to that on the periphery. Mathison (1911) showed that potassium salts, which dilate the arterioles of perfused organs, when injected into the peripheral end of a carotid artery, so that the direct depressant action on the heart is delayed, cause a rise of blood pressure.

#### *EFFECTS OF GRAVITY.*

It was noticed by a French physician, Piorry (1826), that the circulation in the brain in cases of syncope in man could be restored by placing the patient in the horizontal

position. He concluded that the action of gravity on the circulation is of great importance and especially in weak states of health.

Other investigators observed the effect and experimental research on the question was made by Leonard Hill (1895) and by Hill and Barnard (1897).

It will be clear that if the position of an animal is changed from the horizontal to the vertical position head upwards, the arterial pressure in the vessels of the brain will be lowered if the blood vessels in the lower part of the body allow themselves to be distended by the hydrostatic pressure of the column of blood upon their walls. Figure 60 shows that the pressure in the aorta of the dog is lowered by this procedure. Pressure on the abdomen shows, by restoring the blood pressure, that blood has drained into the vessels of the abdominal viscera. Figure 30 p. 60 above), on the other hand, shows that in certain monkeys, this mechanical effect is compensated by some means, or even over-compensated. The compensation, although incomplete in the dog, is shown to have been active by the fact that on return to the horizontal position, the blood pressure rises temporarily above its original level. The chief factor in this adjustment was shown by Hill to be constriction of the blood vessels. He refers only to the splanchnic area, but no doubt the effect was of a general character. Increased respiration played a part, although a subsidiary one.

A point of interest is the situation and nature of the receptors for the stimulus exciting this reflex. If the receptor endings of the depressor nerves are normally under constant stimulation by the blood pressure, it may well be that, when this pressure falls by draining of blood into the regions at a lower level, the depressor stimulus ceases and the centres causing vaso-constriction come into play,

being released from inhibition. On the other hand, Leonard Hill (1900, p. 136) propounds the view that the vaso-motor centres are sensitive directly to changes in the pressure of the blood supplying them. A fall of pressure provokes vaso-constriction, a rise, vaso-dilatation, in a way analogous to the effect of changes in the temperature of the blood on the heat centres in the corpus striatum. The fact that,

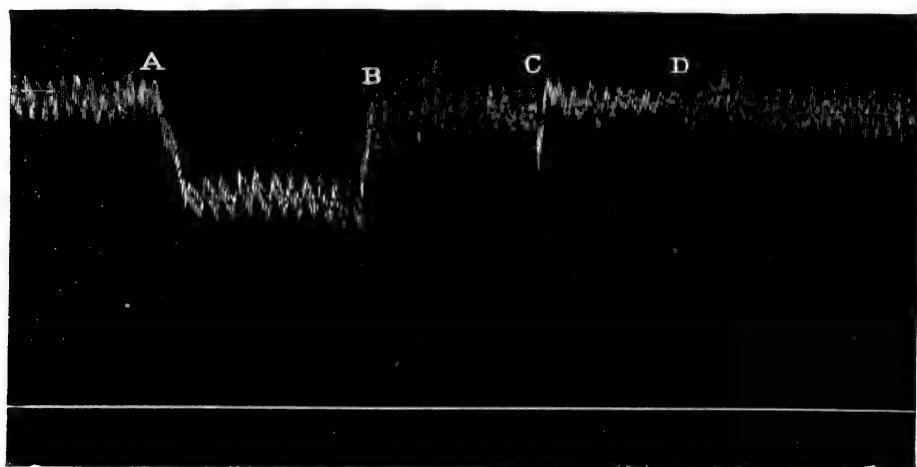


Figure 60.

Effect of Gravity in the Dog.

Carotid canula in the axis of rotation.

A. Vertical feet down.	B. Horizontal.
C. Vertical feet up.	D. Horizontal. (L. Hill, 1895, p. 23.)

From "Practical Physiology" by Pembrey & others (Edward Arnold & Co.).

in the tracing of Figure 30, the compensation is present although the vagi were cut suggests that integrity of the depressor fibres is not essential. But the depressor may possibly have been a separate nerve in this case, although it appears to be included in the vagus trunk in man.

The view that the centres respond to changes in the blood pressure in the vessels supplying them is supported by the observations of Hédon (1910). The cerebral end of

one carotid in a dog (A) was connected to the heart end of that of another dog (B), so that a rise or fall in the

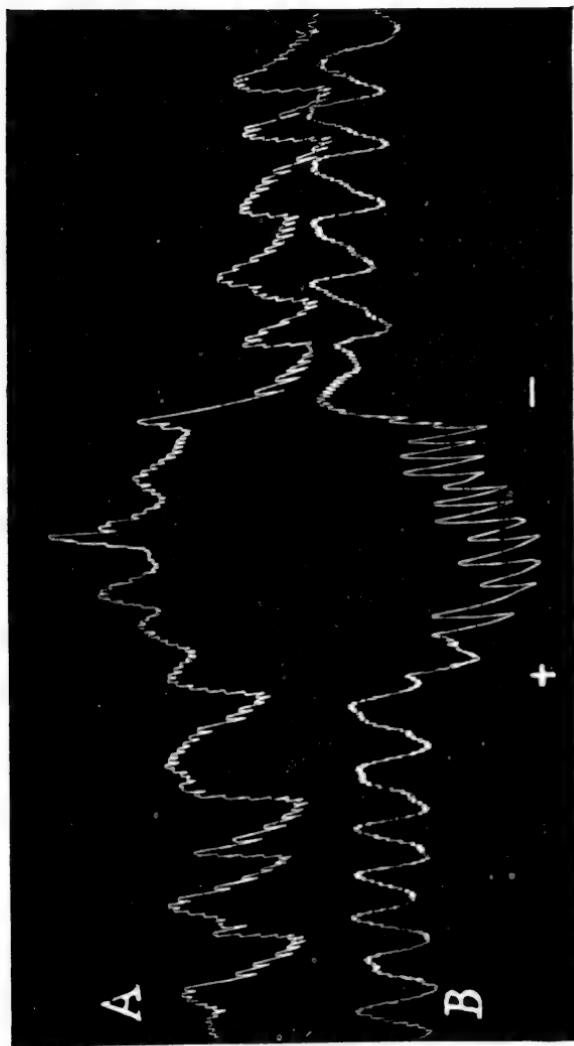


Figure 61.

Stimulation of Vaso-constrictor Centre by Fall of Pressure in its Arterial Supply.  
Femoral pressures of two dogs in crossed carotid circulation. From + to -, stimulation of peripheral end of vagus in that dog which supplied the centres of the other. (Hédon 1910.)

arterial pressure of B would be immediately felt by the nerve centres of A. If any effect on the arterial pressure of A were the result of blood flowing from one to the other, it would be in the same direction in both. In point

of fact, it was found that a rise in B caused a *fall* in A and a fall in B caused a rise in A (see Figure 61). Hence it appears that vaso-constriction is produced by a fall in the pressure in the cerebral arteries and dilatation by a rise.

The changes to which the centres are sensitive may be either the pressure itself or of a chemical nature, as by variation in oxygen supply.

## CHAPTER V.

### *CHEMICAL AND PHARMACOLOGICAL ACTION ON ARTERIOLES.*

We pass on to the discussion of the arterial constriction and relaxation brought about by the direct action on them of chemical substances.

The effects to be considered are those upon the muscular tissue itself or on the myo-neural junctions and is one part of the general action of such substances on smooth muscle. The case of the capillaries is of a different nature and will be discussed in the next chapter.

The importance of the effect of the products of tissue activity on the blood vessels of these tissues was pointed out by Gaskell (1880, p. 68). His work on the vaso-motor mechanism of the voluntary muscles (1876) had convinced him that acid substances produced in their contraction had a direct action on the blood vessels, causing the muscle of the arterioles to relax. Accordingly, he investigated (1880) the action of acids and alkalies on the heart and blood vessels of the frog, showing that lactic acid caused dilatation and sodium hydroxide contraction. At a later date (1901), I showed that carbon dioxide acts in the same way as lactic acid (see Figure 8 above). Carbon dioxide is a product of oxidation in all kinds of cells, whereas, so far as evidence goes, lactic acid is a normal product only in the case of muscle. Or perhaps it would be more correct to

say that the lactic acid stage of the metabolism of carbohydrate is rapidly passed through in tissues other than muscle, except in conditions of defective oxygen supply. Barcroft (1914) suggests that substances similar to the histamine of Dale and Laidlaw (1910) are produced in the metabolic changes of activity. These substances will be referred to in more detail in the following chapter. It will suffice to mention here that their action on arterioles, as on smooth muscle in general, is a constricting one; the dilator effect is on the capillaries. Hence, in themselves alone, they would not bring about a better blood supply to the cells, or not to any important degree, unless there were a simultaneous dilatation of arterioles, by the action of acid or of vaso-dilator nerves. Figure 23 (p. 47 above) shows that the increase in blood flow produced by histamine is small, compared with that of a vaso-dilator acting on arterioles, such as acetyl-choline. Reid Hunt (1918), indeed, suggests the possibility that this latter substance, or one related to it, might be produced in cell metabolism. Carbon dioxide appears to be the chief chemical agent in bringing about increased blood supply to active tissues. It is very doubtful whether histamine-like substances are normal products of cell metabolism. To produce them means a disintegration of certain nitrogenous constituents of the cell and there is no evidence of any increase of nitrogenous metabolism in the normal processes of cell life. It is possible, however, that histamine might be produced by the decarboxylation of histidine already present in the cells or the blood. On the other hand, histamine-like compounds may well be the cause of the fall of blood pressure produced by intravenous injections of boiled extracts of various organs and tissues (Vincent and Sheen, 1903), since Abel and Kubota (1919) have shown that crystalline substances showing the chemical and physiological characters of histamine are

produced even by comparatively mild treatment of certain proteins. Further, we must not forget that a very minute amount of these active substances might suffice when formed in immediate contact with the blood vessels.

Although "metabolites" doubtless play an important part in bringing about an increase in the blood supply of active tissues, their action is almost certainly supplemented by vaso-dilator nervous reflexes. When Barcroft (1914, p. 137) says that we know of no reflex mechanism by which the pancreas, when it enters into activity, "can beg a supply of blood from the vaso-motor centre", he overlooks the stimulation of proprio-ceptor nerves in the organ, a stimulation leading to the Lovén reflexes described above (p. 86). The dilator reflex, moreover, may not be from the organ itself, but from some other organ physiologically connected with it. In the case of the pancreas, from the duodenum or stomach.

An observation by Anrep (unpublished) shows that increased activity is not necessarily accompanied by marked vaso-dilatation. If the pancreas is excited to activity by means of a secretin preparation which has been deprived of its depressor constituent (histamine, Barger and Dale, 1910), vaso-dilatation is scarcely to be detected. It might be suggested that such a direct chemical action on the cells does not involve stimulation of receptors giving rise to vaso-dilator reflexes.

There seems no doubt that the action of carbon dioxide and of lactic acid is due to the *hydrogen-ions* present in their solutions. In my experiments on the frog's leg, the effect produced by a saline solution (without bicarbonate) saturated with carbon dioxide was about the same as that of a lactic acid solution containing one part in 10,000. The hydrogen-ion concentration of these would be about the same and of a value between  $10^{-4}$  and  $10^{-3}$  normal.

The OH ions of *alkaline* solutions have a constricting effect.

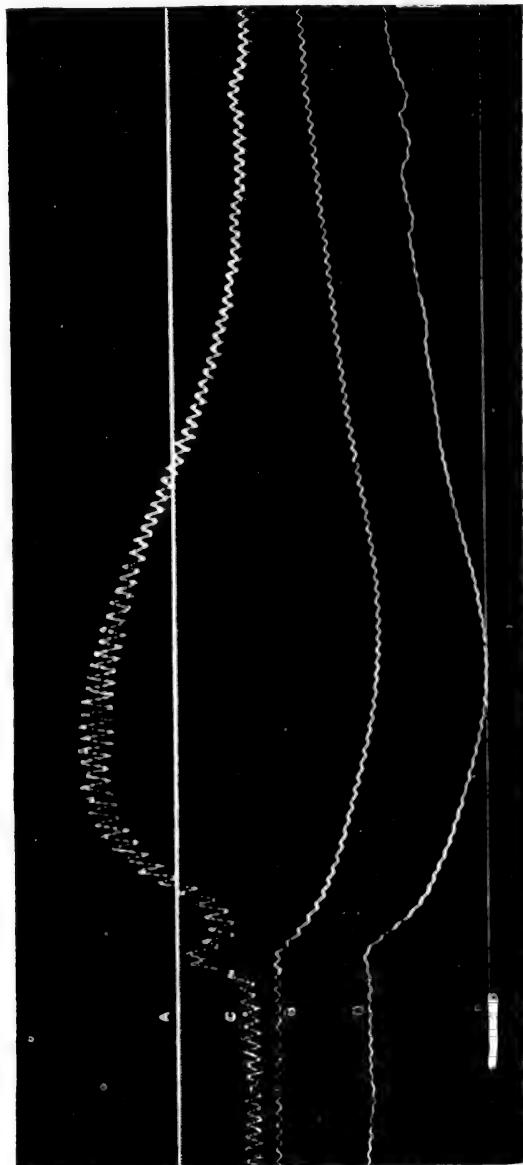


Figure 62.

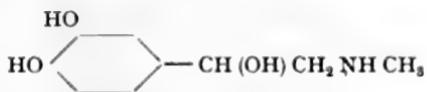
Action of Adrenaline.

- A. Time marker in seconds.
- B. Volume of left forelimb, nerves intact.
- C. Arterial pressure.
- D. Volume of right forelimb, nerves cut.
- E. Zero of blood pressure and signal for injections of adrenaline. (Oliver and Schafer, 1895.)

The results of Gaskell and myself were confirmed by Hooker (1912) and extended to certain metallic ions (1911).

As might be expected from Ringer's experiments on the frog's heart, *potassium* relaxes, *calcium* causes arterial muscle to contract. The action of calcium is shown in a more marked degree by barium. The action in these cases is exercised on the cells of the muscular coat directly, contrary to that of adrenaline, to which we may turn next.

*Adrenaline.* Reference has already been made to the great rise of blood pressure brought about by small doses of this powerful substance, together with the fact that the effect is due to its action on the endings of vaso-constrictor nerves. The action on the blood pressure produced by extracts of the supra-renals and the cause of the rise by peripheral constriction was discovered by Oliver and Schafer (1895), (see Figure 62). This action is confined to the medulla of the gland and the actual constituent, adrenaline, to which it is due, was isolated in 1901 by Takamine. It has the constitution:



a methyl-amino derivative of pyrocatechol.

(*Note.* Adrenaline should be spelled with a final e, according to the recommendation of the Chemical Society with respect to substances known to be organic bases. Active principles of unknown constitution, such as secretin, should have no final e.)

Adrenaline is an intensely active substance. Pysemsky and Kravkov (1912) found that one part in 250 millions of Ringer's solution caused vaso-constriction when perfused through the ear of the rabbit.

The cells which secrete adrenaline stain brown with potassium bichromate and are hence called "chromaffine". They are found in various situations in both vertebrates and invertebrates, in addition to the definite suprarenal bodies

of the former; in the lamprey, they are arranged in masses segmentally. According to J. F. Gaskell (1914, 1919), segmental ganglia of the leech contain nerve cells which secrete adrenaline and the developement of the chromaffine masses in the animal series corresponds with that of a contractile vascular system, while the adrenaline-secreting, chromaffine cells together with the sympathetic nervous system of the vertebrate are to be regarded as both arising from the chrom-affine nerve cells of the invertebrate. The medulla of the suprarenals was shown by Balfour (1878, pp. 242—245) to have the same embryonic origin as the sympathetic nervous system and Kohn (1902) showed that these cells of the medulla arise from a series of groups of cells in connection with the sympathetic along the body axis. Scattered remains of these groups are found in the adult and called "paraganglia", but the main mass concentrates to become the suprarenal ganglion or medulla of the suprarenal body.

As well-known, one of the characteristics of the sympathetic outflow is the connection of each fibre with a second neurone before reaching its destination. Elliott (1913, 3) has shown that the nervous supply to the suprarenal medulla has no cell station previous to that of these cells themselves, a further indication of the similarity of the cells to those of the sympathetic ganglia. Elliott (1913, 1) points out that there are two types of cells to which the sympathetic outflow from the spinal cord proceeds; — (1) those of the sympathetic ganglia, which are distally connected to smooth muscle cells by their axons and thus convey nerve impulses and (2) the medullary or paraganglion cells, not directly connected with smooth muscle, but secreting a chemical substance into the blood and thus producing a stimulation of the muscle or other structure by acting on the junction of the nerve fibre with the cell. It is difficult to realize how this double mode of stimulation came to pass, but Elliott

suggests that the components may have been originally parts of the same process and that the liberation of adrenaline was an essential part of the nerve impulse. His general scheme is given in Figure 63 (see p. 118).

It was first pointed out by Langley (1901, p. 256) that the various effects produced by adrenaline are just those produced by stimulation of the sympathetic supply to the organs or tissues concerned. Elliott (1905) investigated the question in further detail. The fact that the smooth muscle of the intestine reacts to adrenaline in an opposite manner to that in which the arterial muscle does suggests that the effect is exerted on some structure which is not the muscle itself. Since the reaction is not abolished by degeneration of the nerve fibres, the structure in question must be in intimate connection with the muscle and be in trophic dependence upon it (see Elliott, 1905, p. 429). Elliott introduced the name "myo-neural junction" to indicate this constituent of the cell, which is not the ordinary nerve-ending of the histologist, but is on the muscular side of this structure. It is, however, in intimate relation with the connection of the nerve with the muscle; determining in fact the way in which a particular nerve fibre influences the contractile structure, whether by excitation or by inhibition. Since there are similar arrangements in the case of cells other than muscular, such as gland cells and, probably, capillaries, a more general name is needed, perhaps "cyto-neural junction" or "receptive substance" as used by Langley.

Various states which involve stimulation of the splanchnic nerves cause, as would be expected from the splanchnic innervation of the suprarenals, a discharge of adrenaline into the blood, bringing about a rise of blood pressure and the other results of sympathetic stimulation. This was shown especially by the work of Elliott (1912) and of

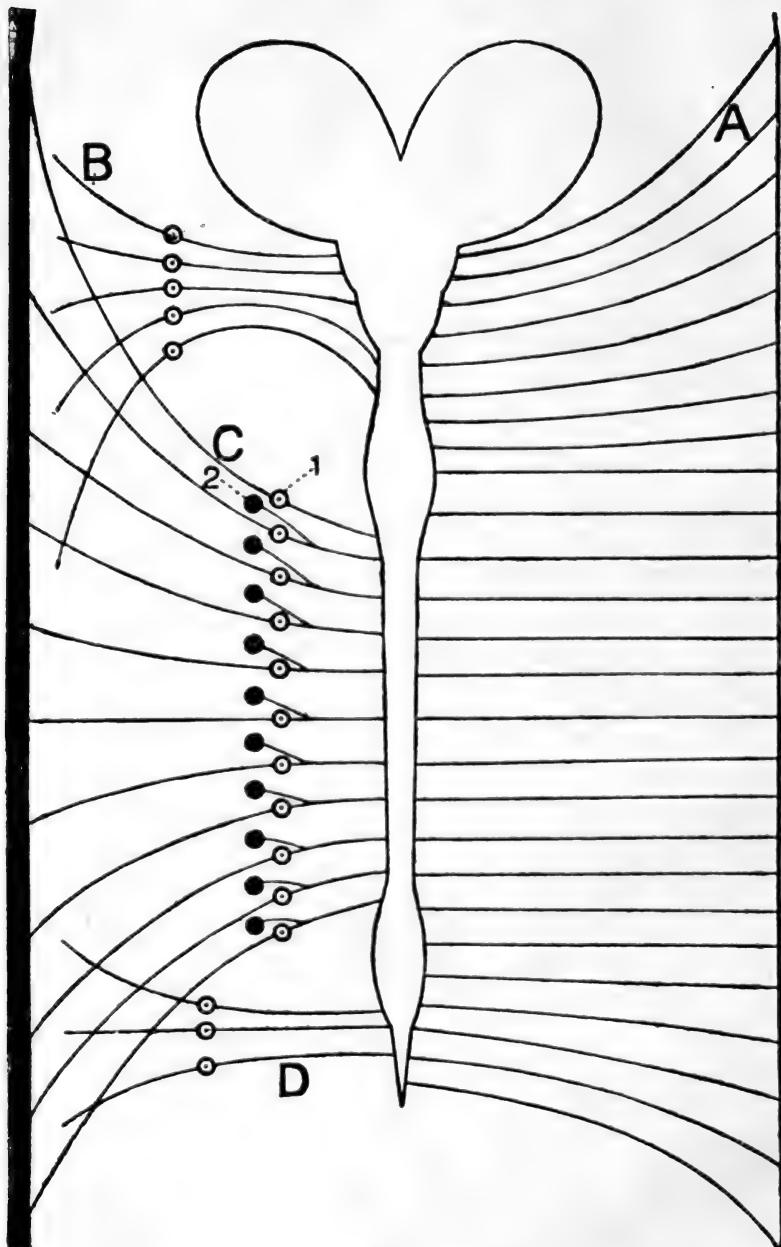


Figure 63.

Diagram of the Efferent Nerves from the Central Nervous System in the Mammal.  
(Elliott, 1913, 1, p. 313 "Brain": Macmillan & Co. Ltd.)

Cannon (1915). The states referred to are fright, anger, anaesthesia, stimulation of afferent nerves and so on. This being so, the question naturally arises whether the rise of blood pressure resulting from stimulation of an afferent nerve may not be entirely due to the discharge of adrenaline. When the peripheral end of a splanchnic nerve is stimulated, the rise of blood pressure takes place in two stages. After a preliminary rise, there is, after an interval, a second further rise. Anrep (1912) showed that the first is a nervous stimulation of vaso-constrictors; the second, a result of adrenaline discharge. In the absence of the suprarenals, the first only is present. The fact that it remains, however, shows that there is a stimulation of vaso-constrictor nerves apart from increased production of adrenaline. Bazett and Quinby (1919), in their cross-circulation experiments, found, indeed, that the nervous mechanism in reflex rise of blood pressure was greatly preponderant over chemical or mechanical factors.

Certain drugs, such as nicotine and pilocarpine, cause stimulation of the splanchnic endings, so that adrenaline sent into the blood has to be taken account of in their modes of action. Dale and Laidlaw (1912, 2) found that the action of these drugs on the cat's uterus was absent in the case of the excised organ. Also, the dilatation of the pupil by nicotine was absent if the suprarenals were eliminated.

Explanation to Figure 63.

*A.* The non-ganglionated ordinary motor nerves to striped muscle, distributed segmentally only. Omitted for simplicity on the left side, where only the ganglionated visceral nerves to plain muscle are indicated.

Of these latter, *B* is the crano-sacral outflow in the vagus, etc.

*C* — the thoracico-lumbar, or sympathetic proper.

*D* — the sacral outflow, or pelvic visceral to bladder, etc.

*C. 1.* — sympathetic ganglion cell. *C. 2.* — the paraganglion cell, secreting adrenaline. The black rectangle represents the mass of plain muscle which is also stimulated by adrenaline from *C. 2* in addition to its innervation by *C. 1.*

Since the suprarenals are excited by splanchnic stimulation, the problem arises as to whether the normal blood pressure is maintained to any important degree by continuous inflow of adrenaline. On the whole, the evidence seems to be in favour of the view that this is too small to have any notable effect of the kind. We have already seen that the action of the smallest effective doses is to cause a fall of blood pressure. The experiments of Dale and Richards (1918) indicate that this fall is due to a dilatation of capillaries and will be discussed in the next chapter.

The results obtained by Gley and Quinquaud (1918) and by Stewart and Rogoff (1917, 1920) show that, under the conditions of their experiments, even stimulation of the splanchnic nerves does not result in any detectable increase of adrenaline in the general circulation. The further evidence, however, brought forward by Cannon (1919) and by Kellaway (1919) in favour of an effective outflow of adrenaline induced by stimulation of the splanchnic owing to pain, asphyxia or excitement shows that there were, in their experiments, some conditions present that appear to have been absent in those of the first-mentioned workers. It is difficult to express any opinion as to the cause of these conflicting results. In delicate experiments of this kind, a positive result might be regarded as of more significance than a negative one. Is it possible that the adrenals were already more or less discharged by some circumstance overlooked in the experiments of Gley and Stewart?

*Pituitary.* Extracts of the posterior, nervous, lobe of the hypophysis excite smooth muscle in general to contraction, including that of the arterioles. We have thus a second natural hormone which causes a rise of blood pressure. Its effect is usually somewhat more prolonged than that of adrenaline and, unlike this compound, a second injection produces a fall of pressure (Figure 64).

We have met with a reversal of this kind in the case of strychnine, where the most satisfactory explanation was found to be that the process normally resulting in inhibition was reversed to an excitation, in combination with a paralyzing effect of the first dose on certain neurones on the

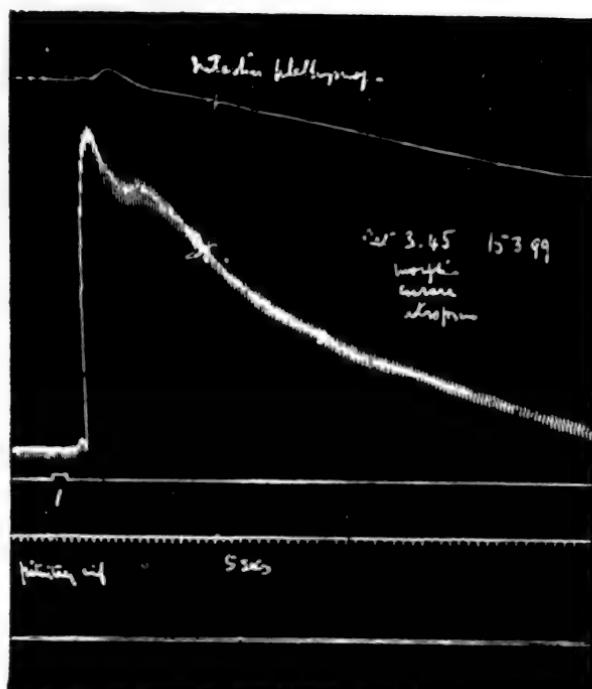


Figure 64 (1).

Effect of Posterior Lobe of Pituitary.

Upper tracing — volume of Intestine.

Lower tracing — arterial pressure.

First signal line — injection of pituitary extract.

Second do. — time in five seconds.

Lowest line — zero of blood pressure.

After atropine. (Schafer and Vincent, J. Physiol. 25, pp. 92, 93.)  
[Cont'd in Fig. 64 (2) next page.]

afferent side. Whether a similar explanation would hold for pituitrin, or whether the effect is more like the peripheral reversal effects to be mentioned below is uncertain.

Turning next to chemical agents not normally produced by the animal organism, we may consider first those which, like adrenaline, act on the sympathetic system.

*Ergotoxin* was prepared by Dale (1906) from ergot. It has the remarkable property of exciting and then paralyzing the motor effects of the sympathetic system, including the stimulation of gland cells as brought about by adrenaline,

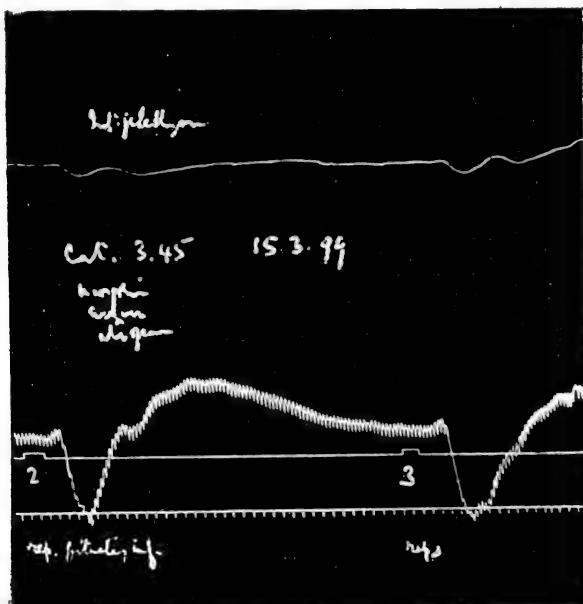
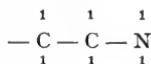


Figure 64 (2).

eaving the inhibitory ones untouched. Thus, the vaso-constrictor effects are abolished, while the inhibitory effect of the splanchnic on the muscular coat of the small intestine remains. If a nerve trunk contains both kinds of sympathetic fibres, we have a means of detecting the presence of inhibitory nerves, even when their effect is normally masked by the simultaneous stimulation of the excitatory fibres.

*Sympathomimetic Amines.* Barger and Dale (1910) have found that an action on the sympathetic system simulating

that of adrenaline is possessed by a large number of amines, even as simple as primary fatty amines, such as amyłamine. It was impossible to discover any chemical complex common to these, except so simple a one as the group



which is also present in many bases having no action on the sympathetic. But their activity and specificity increase as the structure approximates to that of adrenaline. Thus the optimum carbon skeleton is that of a benzene ring with a side-chain of two carbon atoms, the terminal one bearing the amino-group. It is of interest to note that excitatory and inhibitory activity may vary to some extent independently. Thus, the catechol bases with a methyl-amino group, including adrenaline, show the inhibitory effects more powerfully; while the primary amines of the same series have the excitatory property more pronounced.

One of the most interesting of these bases is para-hydroxy-phenyl-ethylamine, or "tyramine", which is produced by decarboxylation of tyrosine and therefore present in putrefying solutions of proteins (see Barger's monograph, 1914, p. 27). Its activity in raising the blood pressure is about one-twentieth of that of adrenaline.

The amine obtained by decarboxylation of histidine, "*histamine*", acts directly on all smooth muscle cells, producing contraction. Thus, by itself alone, it would cause a rise of blood pressure, as it does in the rabbit. In the cat, dog and monkey, the effect is complicated by a powerful dilatation of the capillaries, to be described below.

*Acetyl-Choline.* In 1906 Hunt and Taveau described as a sensitive test for choline its conversion into the acetyl-derivative, which was found to have an intense effect in lowering the blood pressure. Dale (1914) discovered its

presence in extracts of ergot and pointed out that its vaso-dilator action was exercised on the bulbo-sacral outflow of visceral nerves and not on the sympathetic. Although it is devoid of action on the sympathetic, its powerful effect on the vaso-dilators of the skin shows that its action is not altogether limited to the bulbo-sacral outflow, in the sense of being a test for this mode of innervation, as suggested by Gaskell (1916, p. 62), unless indeed one is prepared to include antidromic innervation in the system referred to.

Its activity is remarkable. It is a hundred times more active in producing a fall of pressure than is adrenaline in producing a rise. In 1918, a detailed investigation by Reid Hunt himself was published.

This investigator was at first inclined to attribute the fall of blood pressure largely to vagus inhibition of the heart, especially in view of the fact that its action is paralyzed by atropine. This alkaloid was not known to paralyze vaso-dilator nerves. Dale, on the other hand, held that vaso-dilatation is a large factor in the effect and Hunt in his later work confirms this view.

The peripheral parts of the body, especially the skin, take a larger share in the general effect than the abdominal viscera do, but this is probably merely because of the relative preponderance of dilator nerves in the former, as already mentioned above.

That the effect is exercised on some constituent of the system other than the muscular tissue itself directly is confirmed by the fact that acetyl-choline may cause a dilatation of a limb at the same time as a decrease in volume of the liver, this latter being a passive effect of the fall of blood pressure, owing to absence of active dilatation in this organ. Nitro-glycerin, on the other hand, causes dilatation of both, since its action is on the muscle directly. The fact that, as Reid Hunt shows, the dilator action of acetyl-choline

is abolished by a dose of atropine which has no effect on the result of stimulation of vaso-dilator nerves, demonstrates that the "receptive substance" which is acted on by acetyl-choline and by atropine is not the same as that on which the vaso-dilator nerves act and must apparently be an additional one, on a side-track, as it were. An analogous case is that of the intestinal muscle, as described by Cushny (1918, p. 345). Although atropine prevents the action of pilocarpine on this tissue, it does not paralyze the effects of nerve stimulation.

It is a point of interest that the maximal action of acetyl-choline is on those parts of which the vaso-dilator supply is the antidromic one of the dorsal root fibres.

The action of acetyl-choline is illustrated in Figure 23 (p. 47).

As Reid Hunt points out, although the acetyl-choline dilator mechanism is so powerful, it is impossible to assign to it a "function" in the organism. Unless, in some organ or tissue, choline may be converted into its acetyl-derivative and, if such be the case, an important local effect would be brought about. Thus acetyl-choline might be one of the so-called "metabolites" of active cells; but this possibility remains as yet in the region of hypothesis.

*Nitrites and Nitro-glycerin.* These substances have a powerful vaso-dilator action on arterioles and apparently by acting directly on the muscle cells. Nitro-glycerin acts on account of nitrites being produced by its decomposition.

*Nicotine.* The action of this alkaloid is complex. It first excites and then paralyzes nerve synapses. In the excitation stage, the vaso-constrictor centre and the peripheral synapses of the vaso-constrictor nerves play the preponderant part. There is also a stimulation of the nerve supply to the suprarenals, so that the total effect is a great rise of blood pressure.

*Thujon* (in absinthe) appears to owe its effect in raising the blood pressure to an action on the nerve centres, while

*Cocaine* has a local constrictor action on arterioles in addition to its central one.

*Quebrachine* or "*Yohimbine*" causes a fall of blood pressure from depression of the medullary centres and also a dilatation of the vessels of the skin and genital organs.

#### PERIPHERAL REVERSAL BY DRUGS.

As we have seen, ergotoxin was shown by Dale to paralyze the motor endings of the sympathetic system. After a dose sufficient to effect this, adrenaline, in amount which would produce a rise of pressure in normal animals, has the effect of causing a *fall*.

Similar phenomena were described by Dale, Laidlaw and Symons (1910) in the action of nicotine in the cat, where stimulation of the vagus causes marked acceleration of the heart in certain stages of poisoning; and again by Dale and Laidlaw (1911) in the case of the chorda tympani nerve. After a dose of cytisine, the alkaloid of Laburnum seed, stimulation of this nerve results in no secretion while the stimulation lasts, but is followed by a copious flow. If during this after-flow the nerve is stimulated again, the secretion is temporarily stopped. Langley (1911) showed that, after nicotine or curare, the normal contraction of the bladder produced by stimulation of sacral nerves is followed by relaxation and he regards the hypothesis of unmasked inhibitory fibres as an insufficient explanation.

The dilatation in the hind limb observed by Dale after ergotoxine has been discussed above (p. 35) and the assumption of sympathetic vaso-dilator fibres found to be not altogether satisfactory.

In my "Principles of General Physiology" (p. 428 of the 2<sup>nd</sup> edition) I suggested, on the analogy of the action of

strychnine on the nerve centres, that there might be a similar peripheral reversal effect, such that, e. g., the normal exciting action of adrenaline might be converted into an inhibitory one on the peripheral cell. I was unaware at the time that Anderson had already suggested this possibility to Elliott (see Elliott, 1905, p. 413). Langley, in the paper above referred to, suggests a change in the sign of the movements of ions to and from the cell membrane, a process equivalent to reversal of excitation into inhibition. On this hypothesis of peripheral reversal, the result obtained by Dale and Laidlaw on the *chorda tympani* might be explained as a reversal of the vaso-dilator action into a constrictor one, which would decrease the flow of saliva while it lasted.

This view is at present hypothetical, but receives some support from the observations of Spaeth and Barbour (1917) who show that the melanophores of a fish, *Fundulus*, are contracted by adrenaline and that this action is converted into expansion after treatment with ergotoxin.

#### *SPECIFIC TISSUE RECEPTIVE SUBSTANCES.*

There are certain phenomena which suggest that the arterioles of particular organs may have a special sensibility to some chemical substances. The most marked case is the fact shown by Roy (1881) that urea injected into the blood causes expansion of the kidney, but not of other organs. It is true, as Cushny points out, that it is not safe to postulate vaso-dilatation in the kidney from observations on the volume alone. Any increase in the production of urine would show itself as an expansion of the organ, since the tubules would become more distended. Observations on the blood flow should be made.

The phenomena are in need of further investigation and I refer to them here merely as a possibility. Should

the specific dilatation of the renal vessels by urea turn out to be a fact, I do not think that the explanation given by Gaskell (1916, p. 94) is altogether acceptable. The preponderating evidence is against an active secretion of urea by the tubules and in favour of filtration through the glomerulus. The work of concentration would be less if the glomerular filtrate were more concentrated. Hence, an increased production of vaso-dilator "metabolites" is improbable.

## CHAPTER VI. THE CAPILLARIES.

The questions as to whether the capillaries are capable of active changes in their calibre and whether if so they are under the control of the central nervous system have given rise to some discussion. It is only in recent years that satisfactory evidence with respect to these problems has been brought forward.

The facts that the capillaries consist of a single layer of protoplasmic epithelial cells and are devoid of a muscular coat are not in themselves real difficulties, since we know that cells other than muscle can change their form under stimulation.<sup>1</sup> The pigment cells of the skin in frogs, fish and certain invertebrates may be mentioned and the spherical form taken by the *Amoeba* and by leucocytes are familiar. The sympathetic nerve supply of the melanophores of *Fundulus* has been referred to above (p. 127) and a fairly copious supply of nerves to the capillaries has been described (see Figure 65). At the same time, it must be admitted that it is not quite certain whether any of the vessels in this figure are really capillaries and not small arterioles. Schafer. (1912, p. 346) however, states that gold impregnation of the rabbit's mesentery shows every capillary to be supplied with a nerve running along it, the nerves forming loops.

An examination of the circulation in the web of the frog's foot will impress the observer with two things. He

<sup>1</sup> But see p. 19 above.

will notice how great is the volume of the capillaries in proportion to that of the arterioles and how much greater accordingly is the rate of flow in the latter. Remembering that the friction is proportional to the velocity, he will realize that a change in the calibre of the arterioles must have a great effect on the peripheral resistance and on the pressure on the arterial side of the circulation. But, secondly, he

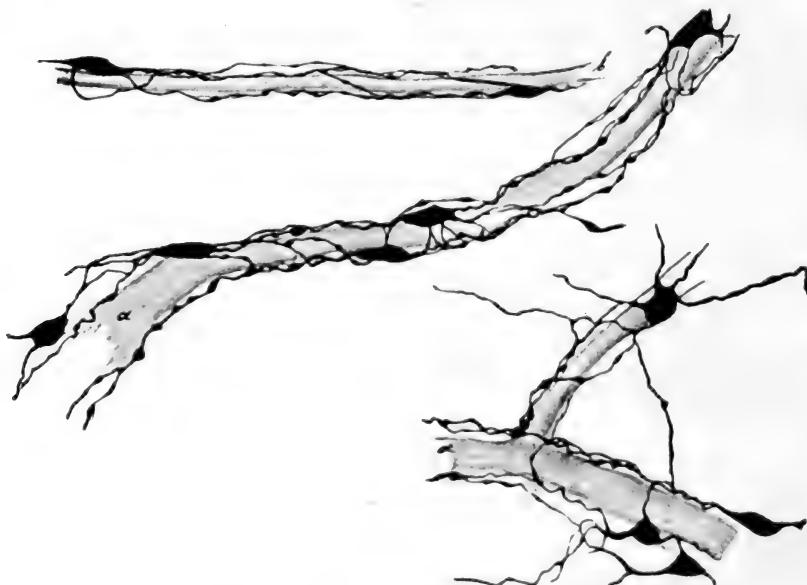


Figure 65.

Terminal Nerve Plexuses around small Blood Vessels (Dogiel).

will appreciate how large is the volume of blood contained in the capillary region and how a comparatively small increase in the diameter of these vessels, if it occurs in a large part of the body, may soak up, as it were, a great proportion of the total blood present in the circulation. As a consequence of this, the amount flowing into the heart from the great veins will be diminished and less will be sent into the aorta. Thus, there will be a fall in arterial pressure and a low supply of fresh oxygenated blood to

the tissues in general. Although the capillaries are wider, the current through them will be diminished, not only on account of the increased width of the stream, but by the lowered driving pressure in the arterioles. Under ordinary circumstances, as described by Lister (1858), Langley (1911) and Krogh (1919, 1920), the whole of the capillaries in a particular region are not filled with blood; some of them are empty and apparently contracted up. They become filled when dilatation occurs during activity of the tissue in which they lie. An additional volume of blood can thus be taken up. Krogh's observations were made on voluntary muscle. He shows that, when resting, only a small number of the capillaries are filled with blood. In activity, a greater or less proportion of the remainder become dilated and convey a current of blood. An important fact is that a comparatively high pressure is needed to open up the collapsed capillaries by passive distension from the arterial side. Hence, if an effective increase of blood supply is required, an active dilatation of the capillaries, in addition to that of the arterioles, must occur. If the latter alone takes place, a more rapid current passes through those capillaries which are open, but a large part of the tissue does not benefit. On the other hand, if the capillaries alone dilate, there is little or no increase in the total supply and the blood which continues to flow is greatly reduced in its velocity and there is a tendency to stagnation and rapid loss of oxygen. This condition will obviously be exaggerated if the arterioles are simultaneously constricted, as happens under the action of histamine, in comparatively large doses, as we saw (p. 123).

That the capillaries are not merely distended or depleted, as the case may be, according to the diameter of the arterioles supplying them, is indicated by the common experience of two different effects of external cold on the skin. The colour of the skin in white races is almost entirely due to

the blood in the capillaries and small veins. When empty of blood, the skin is white and cold. And this may sometimes happen as the result of extreme external cold. The arterioles constrict and the capillaries themselves either do the same or the blood they contained is drained away. But there are also two familiar effects which differ from that mentioned in that the skin is deeper in colour than normal and therefore the capillaries contain *more* blood. In one of these states, which is the normal healthy response, the skin is red and warm; in the other, it is blue and cold. It is clear that the warmth in the former case must be due to an increase in the current of warm blood flowing through the capillaries, and this can only be brought about by a dilatation of the arterioles, probably combined with that of the capillaries themselves. These latter are filled with a rapidly renewed current of fresh warm blood. In this way, the skin is protected from such injurious effects of cold as frost-bite, etc. It would appear that some compromise has to be effected between loss of heat from the body and the safety of the skin. As regards the state of affairs when the skin is blue, it will be remembered that the colour of the veins, as seen through the skin, is blue; so that the blueness of the blood in the capillaries must be because it has lost more oxygen than usual. The current of blood must be very slow, although the capillaries through which it flows are wide. This state of affairs can only be explained by a dilatation of the capillaries in conjunction with a constriction of the arterioles. The skin is cold because there is only a scanty supply of fresh warm blood. An exaggeration of this blue state of the skin may be observed in certain pathological conditions and appears to be easily brought about by cold in such cases.

There is also experimental evidence that the capillaries are able to be affected independently of the arterioles,

although in those cases where the agent has also a dilating effect on the arterioles it is difficult to show that the widening of the former is not a passive one, notwithstanding Krogh's observation that a fairly high pressure is needed to open up collapsed capillaries. Thus Lister in 1858 described dilatation of the capillaries of the frog's web by chloroform and by other agents. It is easy, however, to convince oneself that this drug has a powerful dilating action on the arterioles also. According to Krogh (1920), the local application of urethane dilates the capillaries without affecting the arterioles. Roy and Graham Brown (1880) believed that they had excluded the effect of chloroform on the arterioles by the observation that, if the heart was stopped reflexly during the action of chloroform on the web, the dilated capillaries did not empty. But this is not altogether convincing, because although the capillaries had been previously stretched their elastic reaction might not be great enough to empty them. If indeed there were an elastic reaction it should empty the blood into the arterioles, where the pressure has been reduced to zero. Better evidence of independent action is afforded by the observations of the same authors that the diameter of the capillaries is not in proportion to the arterial pressure. Thus, two capillaries lying side by side may require quite different pressure, applied externally, to obliterate them and, after a pause, that one which previously collapsed with the lower pressure may now require the higher one.

Worm-Müller (1873) showed that large quantities of blood could be injected into dogs without much rise of blood pressure. The blood could be found, post mortem, to have remained somewhere in the vascular system although there was no sufficient distension of the arteries or veins to accommodate it. The conclusion was drawn that the capillaries of the body generally were dilated in

order to receive it. It appears as if a nervous reflex, analogous to or identical with that from the depressor nerve, must be responsible for the result. If a passive distension of the capillaries by dilation of the arterioles is inadequate, we must assume that the capillaries themselves are under direct control of vaso-dilator nerves. Regéczy (1885), however, throws some doubt on Worm-Müller's interpretations of his experimental facts, chiefly on the ground that the latter observer did not sufficiently take into account the filtration of liquid into the tissue spaces.

Doi (1920) finds that in the frog stimulation of the peripheral ends of dorsal roots causes vaso-dilatation in the leg even when the arterioles are maximally dilated by acetyl-choline. Conversely, when the capillaries are maximally dilated by histamine, stimulation of the roots also causes dilatation of the leg. Hence it appears that both arterioles and capillaries are subject to antidromic vaso-dilatation.

Severini (1881) described experiments on the capillaries of the excised mesentery in which carbon dioxide was found to dilate them, oxygen to constrict them. Although Roy and Graham Brown failed to confirm this, it does not seem improbable in the light of later experience and would be an appropriate reaction.

But more important and convincing work on the independent reactions of arterioles and capillaries is that of Dale and Richards (1918). It has been mentioned already that histamine was found by Dale and Laidlaw (1910) to have the effect of bringing about the constriction of all kinds of smooth muscle, including that of the arterioles. But when injected intravenously, into the dog, cat or monkey, the puzzling result of a *fall* in blood pressure was obtained. This, if produced by an action on arterioles, indicates relaxation, and in the case of those drugs which

have a depressor action, it was found to be so. The explanation was not given until the work of Dale and Richards (1918). By a number of ingenious experiments, these workers were able to show that a generalized dilatation of the capillaries, together with absence of effect on or constriction of the arterioles according to dose, is produced. In the first place, plethysmographic records showed a remarkable variability in the amount of expansion of a limb in relation to a given fall of blood pressure, just as would be expected from a conflict between arterial constriction and capillary dilatation in different proportions. Next, it was shown that a purely arterial system, obtained by cutting the mesentery at its attachment to the intestine, was perfused artificially, histamine caused a reduction of the flow by constriction of arterioles. Some very interesting results were obtained by observation of the toe-pads of the cat. If the nerves of one leg are cut in a normal cat, the pads of the denervated side, although the increased volume pulse shows that arterial dilatation is present for some weeks, are *paler* than the normal side, but noticeably warmer. This can only mean that the capillaries are less filled, although a rapid current of warm blood must be flowing through them. The interpretation was confirmed by allowing the two paws to raise the temperature of small amounts of water. The denervated paw warmed the water more quickly than the normal one did. Thus, although the normal paw is more flushed, it is colder; the capillaries must be wider, while the arterioles are narrower. The contrast is similar to that between the "blue" effect of cold and the normal one.

Now what is the effect of histamine on these two states? On the denervated side, it produces increased redness, the capillaries being previously narrow. On the normal side, the first effect is a slight decrease in colour, doubtless due to arterial constriction combined with the

general fall in blood pressure. Later, there is a weak flush, which outlasts the more pronounced effect on the opposite side.

Contrast this with the action of acetyl-choline, an arterial vaso-dilator. The denervated side shows no definite change of colour, because the arterioles are already dilated. The normal side becomes redder than before; the partly empty capillaries are filled up by blood from the dilated arterioles.

It was found that if the contractions of the intestinal muscle, which the direct application of histamine brings about, are prevented by previous application of adrenaline, a redness similar to a capillary flush was produced.

Before passing on to the perfusion experiments, a few words are necessary with respect to the action of *adrenaline*. The fact that a fall of blood pressure is produced by very small doses was referred to above (p. 36). Dale and Richards find that, in such doses, its action is a dilator one on the capillaries; the phenomena are identical with those of histamine, except that the concurrent arterial constriction is more predominant. This effect on the capillaries seems to be something independent of the typical sympathomimetic action of adrenaline. In doses larger than the minimal ones, adrenaline produces constriction of the capillaries, as pointed out by Cotton, Slade and Lewis (1916) and by Langley (1901). Whether this constrictor action implies a sympathetic supply to the capillaries is as yet uncertain.

In their original experiments, Dale and Laidlaw were struck by the fact they were unable to obtain the dilator effect of histamine in the case of artificially perfused organs; the arterial constrictor effect alone appeared. Dale and Richards found that the concurrence of two factors is necessary to enable the capillary effect to show itself. In the first place, adrenaline must be present in the perfusion fluid in sufficient amount to give tone to the capillaries,

and further this tone does not make itself manifest except in the presence of a more copious supply of oxygen than can be carried in a perfusion fluid devoid of haemoglobin. That it is merely a question of haemoglobin as a carrier of oxygen when blood is used is shown by the fact that washed red corpuscles added to gum-saline are equally effective.

A somewhat difficult problem arises as to what the normal capillary tone is due to. The concentration of adrenaline present in normal blood, so far as experimental evidence goes, is insufficient. Capillary tone being necessary for the action of histamine, the fact that denervated organs are more sensitive to the capillary dilator action of this drug than normal ones are makes a nervous origin of the tone improbable.

Some recent observations by Krogh (1919, 1920) are of importance with respect to the nervous supply of the capillaries. He finds that it is possible, by touching with a fine glass needle over the situation of a closed capillary in the frog's tongue, to make this vessel dilate and that the distance to which the dilatation spreads depends on the strength of the stimulus. A similar local effect can be obtained on an arteriole. Degeneration of the nerves to the tongue or the application of cocaine abolishes the effect. The conclusion is drawn that the spreading of the effect is due to an axon-reflex in sensory fibres, analogous to the explanation suggested by myself (1901, p. 196) for the case of the vaso-dilatation produced by stimulation of the peripheral ends of sensory nerves. If this be so, the innervation of the capillaries must be from the dorsal root fibres and the question arises whether the antidromic vaso-dilatation may not be altogether an action on the capillaries, as mentioned on a previous page. Doi (1920) finds that the dorsal root effect is exercised on both capillaries and on arterioles.

The last question in connection with the action of histamine is the method in which capillary dilatation produces a fall of blood pressure, although the arterioles are constricted. Dale and Richards (1918, p. 163) appear to be of opinion that it is due to a decrease of peripheral resistance in the capillary area. From the wideness of the capillary bed, even in normal conditions, it seems improbable that its increase would have much effect on the resistance. The arterial constriction produced by histamine would lower the rate of flow through the capillaries and so make of less effect any dilatation in the latter, although it is to be remembered that the effective dose for arterial constriction is much higher than that for capillary dilatation. The tracing on p. 47 above shows that the increase in the rate of flow is not very great, compared with that of an arterial dilator. On the whole, it seems to me that the fall of blood pressure is mainly a capacity effect, due to the accumulation of a large volume of blood in the dilated capillary region. That even an arterial dilatation may have such an effect was shown by myself in the case of the lowering of venous pressure during stimulation of the depressor (1902, p. 294). This implies a lessened inflow into the heart, however, and Dale and Richards make the statement that the cardiac output is increased under the action of histamine in small doses. I think the question needs further investigation, since, under the action of larger doses of histamine, as will be described in Chap. VIII, the cardiac output is markedly decreased, as shown by Dale and Laidlaw (1919). In some experiments that I have made, the venous pressure showed no change during the fall of arterial pressure, but rose to some extent as the arterial pressure proceeded to recover. The explanation of this behaviour is not clear.

## CHAPTER VII. *THE VEINS.*

Although the muscular coat of these vessels is less developed than that of the arteries, the internal pressure to be overcome by its contraction is much less. When we remember also that the diameter of the large veins is great, we realize that a comparatively small decrease in their calibre would have an important effect in diminishing their capacity. Thus, a contraction of the veins might play a significant part in changes of the total capacity of the vascular system.

It has been held by some physiologists that the veins are almost indefinitely distensible, so that they are capable of accommodating large volumes of blood without perceptible increase of internal pressure. But, although their walls are thin, experimental evidence indicates that they are not very readily stretched. It was found by Roy (1881) that the veins are, in proportion to the changes of pressure to which they are subjected in the organism, less distensible than the arteries. As long ago as 1740, Wintringham showed that veins are less easily burst by internal pressure than arteries are. Gréhant and Quinquaud (1885) found that the veins require, as a rule, a somewhat greater internal pressure to tear them than do the carotid arteries of the same animal. This pressure varied in different individuals from 3.7 to 9.2 atmospheres.

Comparatively little investigation has been made of the vaso-motor innervation of the veins. As in the case of the capillaries, it is a difficult matter to dissociate active changes in their calibre from passive effects due to diminished inflow from the arterioles.

That the veins are, in point of fact, contractile is shown by the rhythmic contractions of those of the bat's wing, as mentioned above, and also by the familiar fact that exposed veins can readily be made to contract up by direct mechanical or electrical stimulation.

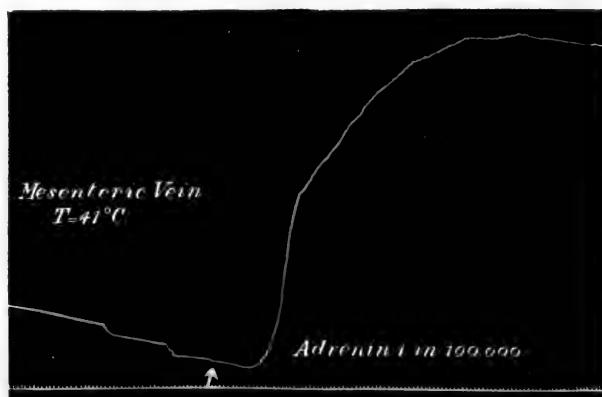


Figure 66.

Action of Adrenaline on a Mesenteric Vein of the Sheep.

Adrenaline applied at the arrow.

(Gunn and Chavasse, 1913.)

As regards their innervation, we have the significant fact that Gunn and Chavasse (1913) found that the muscular coat of all the veins from which they made preparations was caused to contract by adrenaline (Figure 66). This result shows that they receive an innervation of vaso-constrictors from the sympathetic. Thompson (1893) and Bancroft (1898) showed that stimulation of the sciatic nerve caused local contractions of the superficial veins of

the hind leg of the dog. Although the branches of the portal vein in the liver are doubtless in a different case, since they really act as arterioles for the hepatic circulation, it may be mentioned that Mall (1892) showed that they constrict on stimulation of the splanchnic nerves, an observation confirmed by Starling and myself (1894) by stimulating the roots of these nerves. Yandell Henderson (1917) states that, when the intestine is injured, the efferent mesenteric veins contract. This is not a reflex, since it is not abolished by section of the splanchnic nerves. Henderson, Barringer and Harvey (1909) hold that there is a special mechanism controlling the tonus of the veins, such that when carbon dioxide is in excess, the venous pressure is raised and vice versa. This is apparently regarded as in part of nervous origin, since Henderson and Harvey (1918) state that there is "in addition to indirect nervous influences, a peripheral chemical control of the volume of the venous return" to the heart, also by the agency of carbon dioxide. The chief evidence is that if a spinal cat is caused to breathe an excess of carbon dioxide, along with sufficient oxygen, there may be little or no effect on the arterial pressure, but a large one on the venous pressure, in the nature of a rise. The manner in which the rise in venous pressure is brought about is believed to be by a relaxation of peripheral venules. By this means, the intracapillary pressure is lowered, while that in the larger veins beyond the dilated venules is raised. I think that further analysis of this action of carbon dioxide is necessary, especially with reference to the effect of this compound in weakening the cardiac contractions (Patterson). It is possible that the smallness of the rise in arterial pressure in the experiments above mentioned may be accounted for by the heart not beating with sufficient power to raise the pressure against the peripheral resistance. At the same

time, the venous pressure would rise owing to the defective output from the ventricles.

The removal of carbon dioxide by over-ventilation is regarded by Yandell Henderson and his coadjutors as a factor of importance in the production of abnormal conditions of the circulation (1909, 1910). The experiments of Bazett and Quinby (1919) on crossed circulation gave no support to this view. The effects of increased pulmonary ventilation are very complex.

In the experiments of Hooker (1918), a portion of the large intestine was perfused with Ringer's solution while remaining in nervous connection with the remainder of the animal. The arterial canula was then opened to the atmosphere, while that in the vein was connected directly to a manometer. Stimulation of the nerve trunk from the inferior mesenteric ganglion produced under these conditions a marked rise in the manometer, which could only have been brought about by contraction of the veins. Constriction of the arteries would merely press fluid out of the open arterial canula. Under favourable conditions, it was possible to obtain reflex contraction of the vein by stimulation of a sensory nerve and by asphyxia.

The papers by Yandell Henderson on the "veno-pressor" mechanism referred to above (1909, 1910) are also of importance with respect to the general phenomena of venous circulation.

Some old observations by Goltz (1864) may also be mentioned. When the intestines of a frog are repeatedly tapped with the handle of a scalpel ("Klopfversuch"), in addition to inhibition of the heart, there is a maximal dilatation of the abdominal vessels, especially of the veins. If the spinal cord is destroyed, this condition is not recovered from. Goltz concludes that the veins as well as the arteries receive tonic impulses from the central nervous system and

that the venous tonus is as important as that of the arteries. In its absence, the veins might accommodate, without any great increase of tension in their walls, nearly the whole of the blood present in the vascular system. These experiments were repeated by Tawaststjerna (1916), who obtained tracings of the effects. He found that the fall of blood pressure was present after the vagi had been cut and that this prolonged fall was accompanied by a great decrease in the output of the heart.

More systematic investigations of the problem relating to the innervation of the veins were made by Donegan (1921), who found that the veins of the hind limb in the cat and dog receive vaso-constrictors from the abdominal sympathetic. These fibres leave the spinal cord in the lumbar roots from the 2<sup>nd</sup> to the 4<sup>th</sup>. No evidence was found that there is any similar innervation of the vena cava. The veins were found to be apt to pass into a kind of tonic state in which they were completely inexcitable.

## CHAPTER VIII. *HAEMORRHAGE AND SHOCK.*

### *ACCOMMODATION TO CHANGES OF VOLUME OF THE BLOOD.*

Various facts in connection with the way in which the blood pressure is kept more or less at a normal level when additional fluid is added to the blood, or when its volume is diminished by loss, have been already referred to under other headings. It may be useful to summarize them again in a few words.

As regards the nervous mechanism, it is clear that the immediate result of adding blood to a system already adequately filled is to raise the arterial pressure. The receptor endings of the depressor nerve are thus stimulated and a reflex vaso-dilatation is brought about. From the work of Worm-Müller (1873) and of Doi (1920) it would seem that the capillaries share in this dilatation, and not only by passive distension. Owing to the large capacity of this part of the vascular system, it is clear that the part played by the capillaries is of great importance. It should be remembered, however, that Regéczy (1885) points out that Worm-Müller did not allow sufficiently for loss of fluid by transudation through the walls of the blood vessels. It seems desirable that the experiments be repeated with measurements of the volume of the blood.

We have seen above (p. 109) that there is some evidence that the vaso-motor centres are directly sensitive to rise and fall in arterial pressure and that counteracting vaso-dilatation or constriction is thus brought about.

Although the fact that haemorrhage is followed by vaso-constriction has been established experimentally, it is not easy to see what is the mechanism, unless the direct effect on the centres is sufficient. If, however, the depressor mechanism is in tonic excitation from the pressure in the aorta, it is probable that a fall in this pressure would lower the inhibitory influence and the blood pressure would then rise.

It is important to remember that the vaso-constrictor corrective for haemorrhage is, at best, merely a makeshift to ensure a due supply of blood to the brain and heart. As regards the greater part of the body, it can only tend to decrease the already defective supply of oxygen, etc. The only effective remedy is to increase the volume of the blood so that it fills effectively the capacity of the vascular system.

This increase in the volume of the blood is brought about, to a limited extent, by absorption of liquid from the tissue spaces owing to the osmotic activity of the proteins and other colloids of the blood plasma, as pointed out by Starling (1894, 1896). This osmotic pressure is effective, of course, on account of the impermeability of the vascular wall to these colloids. The mechanism of this process does not, however, belong to the subject matter of this monograph. What has been said will suffice to show the necessity of adding to liquids for intravenous injection some colloid, such as gum acacia, of osmotic pressure equal to that of the plasma colloids, if such liquids are to be prevented from rapid escape (Bayliss, 1920, 2).

*Wound Shock.* It was observed, especially during the late war, that wounded men frequently fell into a serious

condition, showing the characteristics of great loss of blood, although there may have been only an unimportant actual haemorrhage from the body. Various evidence pointed to the probability that the injured tissues were producing some toxic substance which had the property of causing vascular dilatation (see especially Quénau, 1919). It was

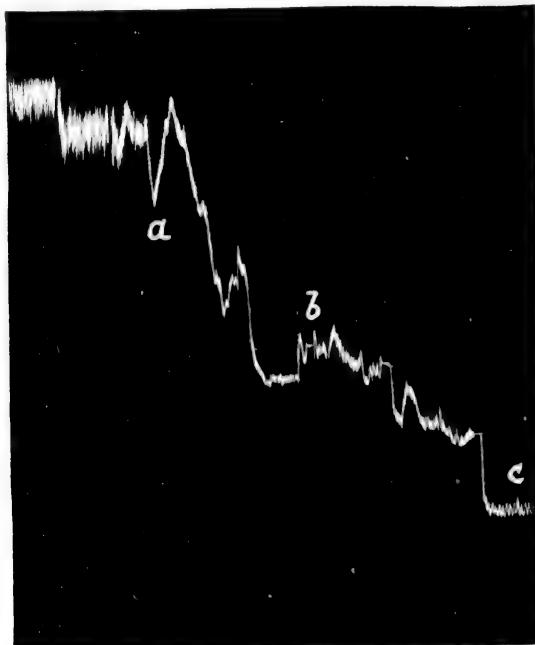


Figure 67.

Fall of Blood Pressure after Injury to Muscles.

a Thighs crushed.

b One hour later.

c Half an hour after b Artificial respiration necessary.

found by Cannon and myself, working conjointly, (see Bayliss and Cannon, 1919; Bayliss, 1918; Cannon, 1919), that the state could be imitated in cats, under conditions in which nervous reflexes were excluded, by crushing the muscles of the thighs (Figure 67). The similarity of the

state to that produced by histamine (Dale and Laidlaw, 1919) is obvious. Although the toxic products from injured tissues have not yet been actually identified, they have the same physiological action as histamine; that is, as pointed out above (p. 135), a widespread dilatation of the capillary vessels, leading to a pooling of blood and its withdrawal from effective circulation. This decrease in effective blood volume has been shown to be present in cases of wound shock. If the state has not been allowed to proceed too far, the defective blood volume can be made up by transfusion of blood or gum-saline and the patient's life saved. If, on the contrary, the "shock" is very severe, or has lasted long, a further cause combines in the production of the deficient volume of blood. The normal impermeability of the capillary wall to colloids is lost. In consequence of this, the osmotic pressure of the proteins becomes ineffective, fluid leaves the circulation and any injected fluid, whether blood or an artificial solution, fails to maintain the volume of the blood and no treatment is of avail.

A point of general importance which has emerged from the work on wound shock is that the primary requirement in any morbid state is to maintain the effective volume of the blood up to its normal value, whether this has been decreased by haemorrhage or by toxæmia. Within wide limits, dilution of the blood by such a solution as gum-saline is of little importance, so that transfusion of blood itself is rarely necessary.



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